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PHYSIOLOGICAL GENETICS

BY

RICHARD GOLDSCHMIDT, PH.D., M.D., D.Sc.
Professor of Zoology, University of California

FIRST EDITION

McGRAW-HILL BOOK COMPANY, INC.

NEW YORK AND LONDON

1938

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PREFACE

This is the third time that I have presented the subject matter of this book. Each time it has been in different form. The first little book, "Die quantitative Grundlage von Vererbung und Artbildung," written in 1917 and published in 1920, consisted of a number of essays in which I developed my views on the problems of gene and development as derived from my own work on *Lymantria dispar*. There was not much material from other sources to be quoted. Ten years later I returned to the same subject. Meanwhile my own work had amplified, experimental embryology had entered a new phase, and a number of other geneticists had become interested in the problems of genic action. Notable among these were S. Wright, whose interest in the subject dates back as far as 1916; Zeleny and his school, who furnished most exact quantitative data; J. S. Huxley, who had contributed to the theoretical analysis and had started experimental work; Sturtevant, who had just cleared up the case of Bar eye in *Drosophila*; and Plunkett, who had applied his physicochemical knowledge to certain problems. This second book, "Physiologische Theorie der Vererbung," was meant to elaborate in all details my own views regarding the action of the gene in development, but it also reported whatever relevant work of others was available. Again ten years have passed, and these have witnessed an ever-growing interest in the field and a correspondingly increasing amount of work, which, with the introduction of new methods, is expanding more and more. As it is emphasized over and over again by writers of texts and by general speakers that we know next to nothing of the action of the hereditary material in controlling development, it seems advisable to present the entire material available. Not only has this material been assembled and reviewed, but an attempt has been made to organize it into the skeleton of a future science of

physiological genetics. Needless to say, the reader is supposed to have sufficient knowledge of genetics and embryology.

The author takes pleasure in expressing his gratitude to Professor E. B. Babcock, who was so kind as to go carefully over the whole manuscript; also to those publishers who permitted me to copy figures.

RICHARD GOLDSCHMIDT.

UNIVERSITY OF CALIFORNIA,
BERKELEY, CALIF.,
January, 1938.

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PHYSIOLOGICAL GENETICS

I. INTRODUCTION

Genetics is the study of heredity. As the causation of all hereditary traits must be found in the fertilized egg (or its physiological equivalent in protista and lower plants), it is the aim of genetics to link the agents within the germ cells with the hereditary traits observed in the fully developed individual. There are two main aspects of this problem: first, the unknown agents in the germ cells have to be identified; their mode of transmission in all its phases has to be ascertained; and the facts found have to be brought in line with the results of genetic experimentation. As is generally known, the study of these problems has accumulated the bulk of facts usually considered as genetics proper, culminating in the generally accepted theory of the gene as the hereditary unit and the chromosomes as its seat. This side of the problem of heredity may be called the problem of the mechanism of heredity, and the work that has solved it is the main content of what is usually called *genetics*. There is a second aspect of the problem of heredity: to understand how the gene, whatever it is, acts in controlling typical development to the adult form showing all the hereditary traits. One might call this problem simply the problem of development. But as development is to be linked specifically with the function and action of the genes, this special chapter may be termed the *physiology of heredity*; and the science devoted to its solution, *physiological genetics*. One might also speak of *static genetics*, studying the status of the germ plasm; and of *dynamic genetics*, inquiring into the acting forces that lead to the visible effect.

The problems of static genetics may be and have been attacked directly, and the laws and rules that have been derived from experiments in this field may actually be made visible in concomitant cytological studies. Physiological genetics, however, does not offer any method of direct attack and therefore calls

constantly for interpretative hypotheses which are sometimes difficult to prove. This constitutes simultaneously the danger and the charm of the work in this line. The effect has been that comparatively few geneticists were attracted to this difficult field and that those who were had to labor in the dark. Thus, the part of genetics that to me is the most interesting was practically banned from advanced treatises and textbooks of genetics, and the opinion has developed and has even been voiced that it is not worth while to mention a field in which nothing is known with certainty. But the history of science teaches us that it is just such borderline fields of today that will bear the fruits of tomorrow. Fortunately the negative attitude has begun to change considerably, and more and more workers of the younger generation are attracted to the problems of physiological genetics. It might therefore be useful to put together the known facts and to link them into a picture, knowing that this picture will be subject to many changes and improvements even in the near future.



II. THE MUTATED GENE AND THE POTENTIALITIES OF DEVELOPMENT

In the following discussions, we take the existence of the gene for granted without further inquiry into its nature, as the facts that we shall have to report and the conclusions to be drawn are largely independent of the conceptions regarding the nature of the gene. One of the basic facts of genetics is, then, that the action of the gene in controlling the typical development of hereditary traits cannot be studied directly but may only be extrapolated from the knowledge of the action of a mutant gene: the existence of the normal or $+$ -gene is only inferred from the existence of a mutant allelomorph showing Mendelian behavior. The action of a mutant gene is a different one from the assumed action of the $+$ -gene; *i.e.*, the mutant gene must control or produce a deviation in the series of developmental processes leading to the visible character. Development, as we know, is, leaving aside the difficult problem of regulation, a process of extraordinary precision. Under constant conditions, one step follows the other with almost invariable precision in regard to space and time. Each step is dependent upon the normal appearance of the preceding one, and the normal result depends—barring regulations—upon the orderly sequence of events in quality, quantity, time, and space. One of the consequences of this situation is that the possibilities of changing the details of developmental processes without injuring the proper cooperation of those processes are rather limited. Most of the changes of individual processes that might be produced will throw out of gear the combined system, and the result will be destructive. But certain processes may be changed without deleterious consequences; and if this is done by a genetic change, we call it a mutation. Such considerations, obvious as they seem to be, make us expect that the action of mutated genes upon development cannot be of a different type from any other changes of development induced by experimental agencies: in both cases, something changes the detailed course of some developmental

process or processes; and in both cases, the quantity and quality of the possible change are limited by the degree of freedom left to the individual developmental processes without destroying their integration into a more or less normal whole.

These considerations show that it is of primary importance for an understanding of the action of the gene to compare the effects of the mutated gene upon development with effects produced by external agencies upon the development of the Wild type.

1. THE PHENOCOPIES

A. DESCRIPTION

In his classic researches upon the wing pattern of butterflies, Standfuss (1896) showed that it is possible to change this pattern by the action of extreme temperature in the pupal stage so that the experimentally produced pattern cannot be distinguished from the pattern of known races of the same species; *e.g.*, heat treatment of the Swiss *Papilio podalirius* could produce a form looking like the variety *P. zanclaeus* found in Sicily. Central European *Papilio machaon* pupae treated with heat gave rise to butterflies resembling the Syrian race *P. sphyrus* or the Turkestan race *P. centralis*. Central European *Vanessa urticae* pupae treated with low temperature produced types like the *V. polaris* from Lapland; and the same treated with heat gave forms indistinguishable from the race *V. ichtusa* of Sardinia (Fig. 1). In this case, the geographic races that were copied in the experiment were known to be constant and therefore presumably genetically different from the main form, though this genetic difference was not established.¹ The facts were used mostly for phylogenetic and Lamarekian speculations, and only in 1917*d*, 1920*b*, and 1927*c* did Goldschmidt point out their importance for the understanding of the action of the gene. Recently Goldschmidt (1935*a*) proposed the term *phenocopy* for such forms, produced experimentally from the Wild-type form, the phenotype of which copies or duplicates the appearance of a mutant (or combination of mutants) of the same form. We shall use this term henceforth.

¹ In other experiments, heat treatment of female pupae produced the male type of wing pattern. Here, of course, as we know now, the normal difference is controlled by genes.

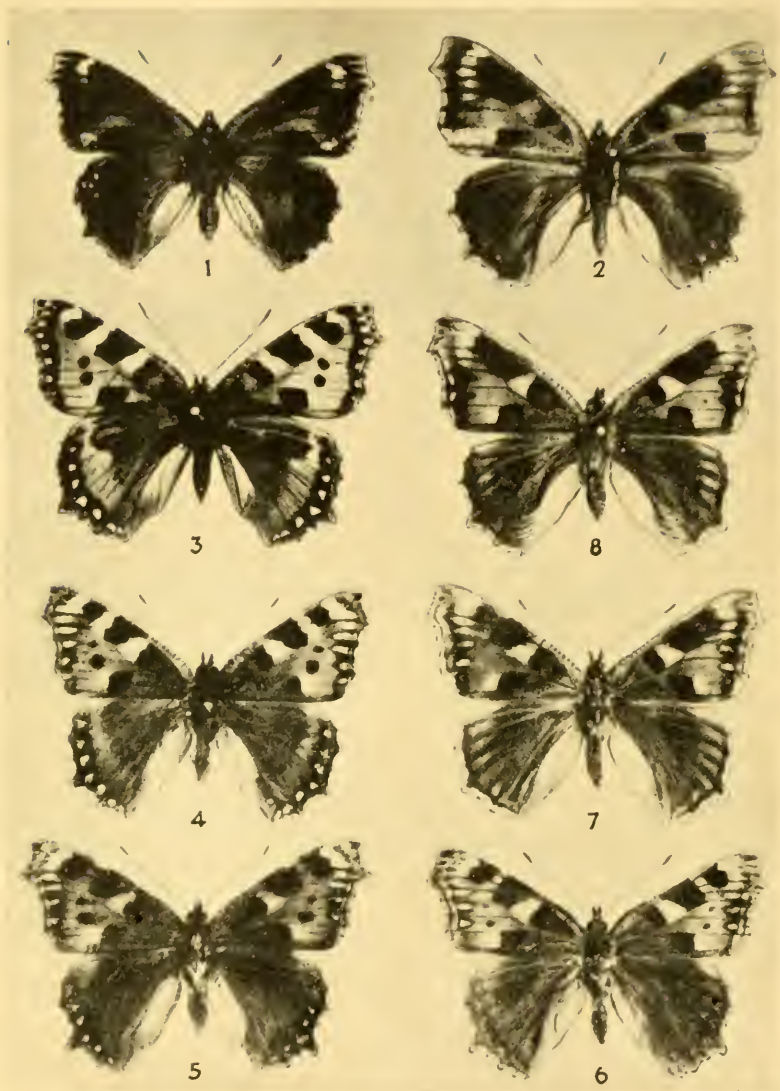


FIG. 1.—1-8, eight different phenotypes produced by temperature action upon the pupae of *Vanessa urticae*; 9, the usual type; 13, 14, the geographic race *ichnusa*; 10, *ichnusa*-like type produced as phenocopy. (Photograph Fischer, from Goldschmidt, *Einf. i. d. Vererbwiss.*, 5th ed., 1929, Fig. 174.)

One of the elementary conceptions of classic genetics is, of course, that one and the same phenotype may be hereditary or only a modification, and examples of this are found in all lines of genetic work. But very rarely has the question been raised

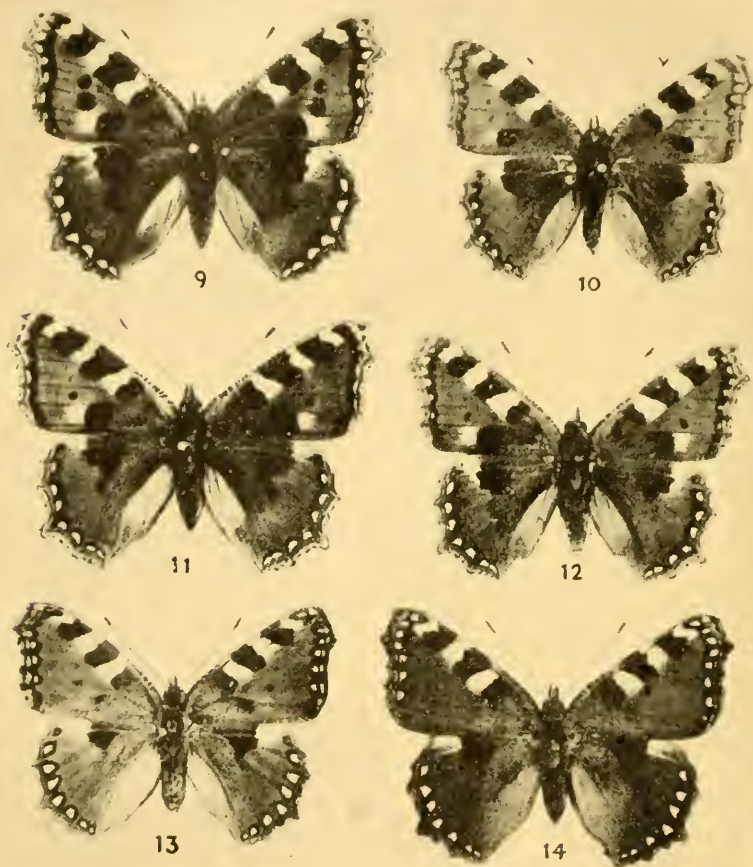


FIG. 1.—(Continued.)

as to whether or not there is a physiological connection between both phenomena, which might be attacked experimentally. Some beginnings are found in the earlier work of Tower (1906), who claimed that in *Leptinotarsa* he could produce mutations or

their phenocopies, according to the way he treated his animals with abnormal conditions. This, however, has never been verified. Beebe's (1907) experiments changing the feathering of the dove *Scardafella inca* by action of moisture also belong here. They resemble Standfuss' experiments in so far as the type was shifted toward the type of a known but unanalyzed geographic race.

The first controlled experiments with genetically known characters were made by Timofeeff (1926), who reported that some mutations found in *Drosophila funebris* were paralleled by identical modifications. In one case, a change of temperature could produce one of these phenocopies, contorted wings.

A systematic study of this problem was inaugurated by Goldschmidt, who reported in 1929*a* that it is possible to reproduce the phenotypic likeness of many mutants of *Drosophila* by treating larvae of a definite stage with temperature shocks, and this in a quite regular manner. The main results as published later (1935*a*) are:

If *Drosophila* larvae of a definite age are treated with temperature shocks of 35 to 37°C., a considerable number of the flies hatching from such larvae are more or less modified. Among these modifications we find many types of abnormalities and simultaneously the phenocopies of numerous known mutations. Among these are most frequently the changes of bristles, copying practically all known types of bristle mutations, *e.g.*, forked, bobbed, stubble; further, the copies of all types of wing mutations like miniature, arc, curly, pointed, dumpy, scalloped; further, the copies of many types of mutation of eye form like small eye, lozenge, star; furthermore, rare but sufficiently frequent copies of different mutants of body form and appendages like aristaless, dachs, abnormal abdomen, and also such types as benign (tumor); more rarely copies of changes in color and design like sooty, trident. All of these phenocopies appear not only in the complete form represented by the well-known mutants but in a series of different grades resembling all types of known multiple allelomorphs or such as are to be expected without having been found. Generally speaking, one might say that all groups of known mutants are represented and a considerable number of individual members of each group. As only one method with not too many variations was used, one might expect that a proper variation of

method would produce the phenocopies of all known mutants (see pages 9 and 10). It ought to be added that in these experiments the modified individual may exhibit simultaneously quite a number of different traits; *e.g.*, the wing might be simultaneously short, spread, rolled, and even the two wings different.

The following details are of importance. Within a rather considerable range of variation, typical effects are dependent upon four variables:

1. Developmental stage at which the heat shock is applied.
2. Time of exposure to heat (6 to 24 hr.).
3. Intensity of heat (35 to 37°).
4. Genetic condition of the material.

It might be said that the number of phenocopies (up to 100 per cent) and the degree of phenocopic change (up to the highest member of a given series) are roughly proportional to the product of the time and the temperature of the exposure, *i.e.*, to the intensity of the shock. The specific type of phenocopy produced is dependent upon the intensity of the shock, the time of its application, and the genetic line used for the experiment. It would be surprising, of course, if so rough a method were to produce a 100 per cent typical result for all different combinations. But it is a fact that, at least for some of the phenocopies, a formula can be given which always produces them within a certain range of variation. Table 1 contains some data as found in a definite series of experiments with the Oregon wild line.

It is further very typical that certain phenocopies tend to appear together with a definite treatment. Thus it is possible to produce quite regularly the combination of spread wings and long (angora) bristles or of curved wings and short stubbly bristles.

The influence of the race is a rather considerable one. Some wild or mutant races respond more easily to the stimulus than others. Some are more apt to produce phenocopies of the bristles; others, with the same method, give more wing modifications. And some of the phenocopies were produced exclusively or almost exclusively within a definite line. We shall return later to this point.

A special interest attaches to the time element, the sensitive or critical period at which the phenocopies may be produced. This important point will be treated in a separate chapter.

Further important facts have been added by other authors. Jollos (1933) confirmed many of the foregoing findings in connection with work in a different line. Gottschewski (1934) found that exposure to cold produced similar effects. This was to be expected on the basis of the classic experiments on butterflies, where Dorfmeister (1864, 1879), Merrifield (1889, 1894), Standfuss (1896), and Fischer (1895) had shown that extremely low temperatures produce the same modifications of the wing pattern

TABLE 1.—PRODUCTION OF DEFINITE PHENOCOPIES UNDER TYPICAL CONDITIONS

Phenotype	Age days	t°	Exposure, hours	Optimum per cent of phenocopies
Scalloped.....	4½-5½	35	12-24	70
Curly.....	6-7	35-37	18-24	76
Ski.....	6-6½	36-37	12	43
Spread.....	5½	35	18-24	91
Curved.....	5-7	36	18	23
Dumpy.....	5	36	12	34
Lancet.....	7	36-37	18	22
Miniature.....	5½-7	36-37	12-18	40
Blistered.....	5-6	36	18	10
Rolled.....	7	35-37	18-24	40
Trident.....	7	35-37	6-24	82
Eye size.....	5½-6	37	18	100
Horns.....	7	35	24	4
Benign.....	4½	35	18-24	75

as high-temperature shocks. In Gottschewski's freezing experiments also phenocopies of the eye-color mutants appeared, which had been absent in the heat experiments. Recently Friesen (1936) reported the production of phenocopies in *Drosophila* by the action of X rays. His results, as far as they go, agree in all the points mentioned with those of the temperature experiments. It seems, however, that some of the phenocopies produced by temperature shocks do not occur in the X-ray experiments, and vice versa.

Here belongs also the report by Bobroff (1930) that X-ray treatment of caterpillars results in males' showing some female characteristics (see footnote, page 4). Geigy (1926) produced

by action of ultraviolet rays abnormal abdomen in *Drosophila*, resembling the well-known mutation.

We have mentioned the fact that occasional phenocopies are found in many cases, apart from the systematic experiments just reported. One of these may be reviewed here because it belongs to a case of special genetic and embryological interest. Another, the experiments of Kuehn and Henke on the flour moth, will be reported in the following chapter.

A well-known hereditary abnormality in fowl is rumplessness, which has been studied genetically and anatomically by Du Toit (1913), Dunn (1925), and Landauer (1928). It consists of a rudimentation of the end of the vertebral column (see page 26). Occasionally also in normal strains individuals are found who exhibit this character in a nonhereditary form (about 1 in 1,000 individuals). Danforth (1932) succeeded in producing this type as a phenocopy in $7\frac{1}{2}$ per cent of eggs treated with varying abnormal temperatures during the first week of incubation. As an explanation he accepts Stockard's views, which will be reported on page 47.

There can be no doubt that similar facts will be found in plants. Numerous examples are known of modifications resembling hereditary types. No systematic attack upon the problem, using known gene mutations, is known, though it might be easily done for floral abnormalities, leaf forms and types, and the like. A hint at such facts is found in Zimmermann (1934).

For curiosity's sake it might finally be mentioned that even certain details of chromosome behavior fall into this group: Genes are known that prevent synapsis of the chromosomes, and the same phenomenon may be produced by action of abnormal temperature (Oehlkers, 1936). There are genes causing abnormal fertilization with consequent gynandromorphism (Goldschmidt-Katsuki, 1927), and the same effect may be produced by temperature shocks (Roesch, 1928).

B. RELATED PHENOMENA

Thus far we have recorded the cases in which the phenocopies of different type were produced from the Wild type. There is another group of experiments, also performed on *Drosophila*, in which the phenotype of quantitatively different members of a

series of multiple allelomorphs was reproduced through treatment of a member of the series. There is first the work of Zeleny and Krafka on the Bar-eye series in *Drosophila*. Seyster (1919) and Krafka (1920) had shown that the size of the eye and the number of ommatidia in Bar-eye *Drosophila* vary with the

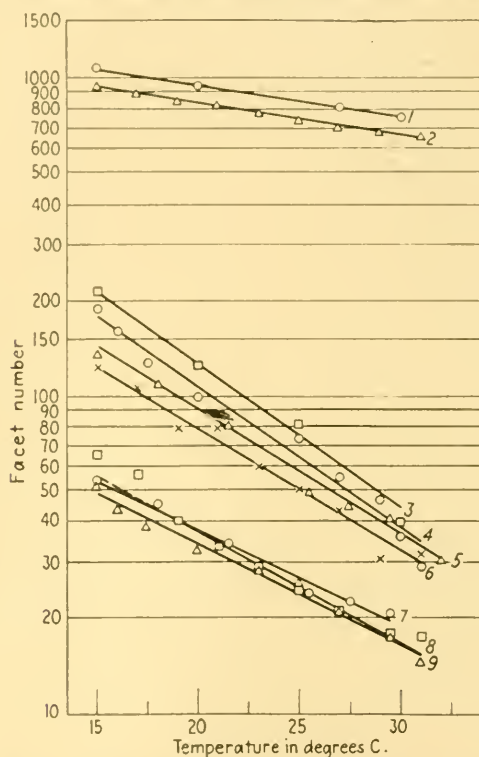


FIG. 2.—Data for homozygous females of various stocks of the Bar-series in *Drosophila* plotted semilogarithmically. 1, Wild type full; 2, reverted full; 3, unselected Bar; 4-6, different low selected Bar; 7-9, different Ultrabar. (From Hersh, 1930, *J. Exp. Zool.* **57**, Fig. 1.)

temperature at which the larvae are developed. On the average an increase of 1°C. produces a decrease of about 10 per cent in ommatidial number. In Ultrabar, the change is about 8 per cent; for Wild eye the effect is about $2\frac{1}{2}$ per cent. In flies heterozygous for Ultrabar and Wild, the percentage is equal to that of Ultrabar. (We shall return to this point in the chapter on dominance.)

More exact measurements were taken by Luce (1926) and Driver (1926, 1931) for different temperatures and alleles. As an

example illustrating our point we reproduce a representation of Hersh's data for different lines of Wild, Bar, and Ultrabar at different temperatures, plotting temperature against the logarithms of facet number (Fig. 2). The point of interest for the descriptions in this chapter is the phenocopic effect in both directions between Bar and Ultrabar: at 15°, genetic Ultrabar resembles genetic Bar at 25°; etc. Just as the Bar series of multiple allelomorphs controls different numbers of ommatidia, so temperature acting upon the larvae shifts the phenotypes within the series of existing or possible allelomorphic phenotypes.

Still more interesting in regard to the analysis of gene action is the work on temperature action upon the wing of the mutant vestigial in *Drosophila*, inaugurated by Roberts (1918) and continued by Harnly (1930-1935), Nadler (1926), Riedel (1935), and Stanley (1928-1935). Roberts was the first to show that an increase in temperature during the larval stage of vestigial flies increased the length of the wing through all the intermediate stages up to a normal wing. Like all his successors he expressed this change in terms of wing length or growth. It is, in fact, something very different, as will be shown later, but for the sake of description and measurement these terms may pass for the present. The point of importance at this juncture is that the stages of "lengthening" of the wing reproduce the phenotypes of the series of allelomorphs of vestigial. More exact data were obtained by Harnly (1930). The following table gives his results in terms of wing length; it has

TABLE 2

Degrees centigrade	Mean length, mm.	
	Male	Female
18.3	0.64	0.61
26	0.66	0.71
28	0.69	0.73
29	0.74	0.74
30	1.00	0.79
31	1.70	1.12

to be added that, with length, breadth also increases and that the general shape of the wing (the amount of scalloping) assumes the

type of the ascending allelomorphic series named strap, antlered, ragged, snipped, notched, and nicked.

It is important to note that between 18 and 29° the temperature effect was very small; a rise from 29 to 30° affected the male wing considerably; and from 30 to 31°, still more (three times as much). In the female, the same happened but began only 1° higher. It ought to be added that general work in temperature effects upon *Drosophila* proves that 29° is about the upper limit of the physiological temperature zone for this animal, beyond which a rise in temperature has an effect upon developmental processes that in general terms may be described as inhibiting. Stanley's work which led to the same results will be discussed in the chapter on the sensitive period.

A still more detailed account has been given by Riedel (1935). She also concludes that the wing of a *vg*-fly becomes more and more like Wild type with the rise of temperature, and she finds definite shapes characteristic for each temperature. Figure 3 (on pages 14 and 15) shows such a series with the temperatures used. Their resemblance to an allelomorphic series is obvious.

In these experiments we are actually facing the reciprocal of the phenocopic effect, showing that at least in some cases the process responsible for the development of the phenotype of a mutation is reversible; furthermore, just as we found that the phenocopies may be produced in a quantitative series imitating a series of multiple allelomorphs, this reversed phenocopic action also produces the phenotypes of the respective multiple allelomorphs of the *vg*-series. We shall return later to this very important point.

C. THE SENSITIVE PERIOD

Half a century ago, the first workers in this field, studying the temperature aberrations of butterflies, mainly with phylogenetic ends in view, made the important discovery that the experiments were successful only if the stimulus was applied during a rather short period of larval life preceding pupation. This period was called the *sensitive*, or *critical*, period. All later studies confirmed its existence and showed its importance for an analysis of the problem. We shall describe the facts using the same examples as before with the addition of new cases.

It has already been stated that the production of phenocopies in *Drosophila* succeeded only if the temperature shock was applied at a definite time in development, the sensitive period. It could be shown (Goldschmidt, 1935a) (1) That some of the phenotypes could be produced only during a rather short period; *e.g.*, the

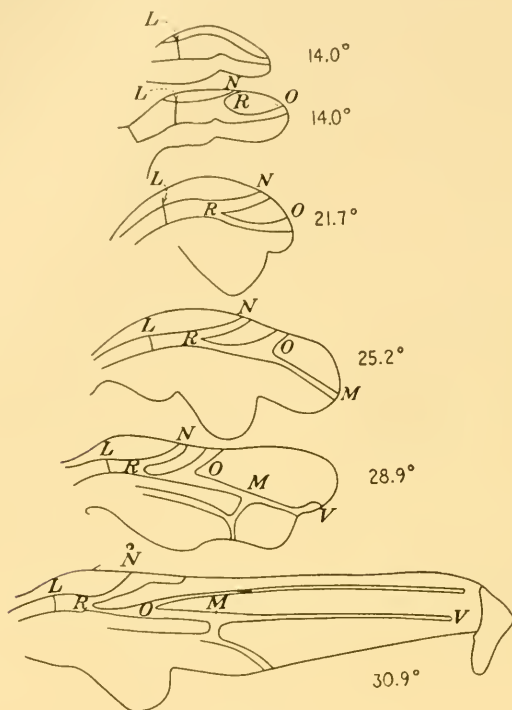


FIG. 3a.

FIG. 3.—a, *vg*-wings at different temperatures; b, *vg* male wings at 32.9°C. (1st col.) and at 34° (2d and 3d col.). (From Ridel, 1934, *Arch. Entwicklgméch.* **132**, Figs. 12, 13.)

type with scalloped wings can be produced only during a short period preceding pupation; (2) that other phenocopies may be produced over a rather considerable stretch of time in development, provided that a sufficient stimulus is provided; (3) that the sensitive periods of different phenotypes may overlap; (4) that the sensitive periods *ceteris paribus* are different in different races. Table 3 gives the results for a few types in percentage of obtained phenocopies in one experiment.

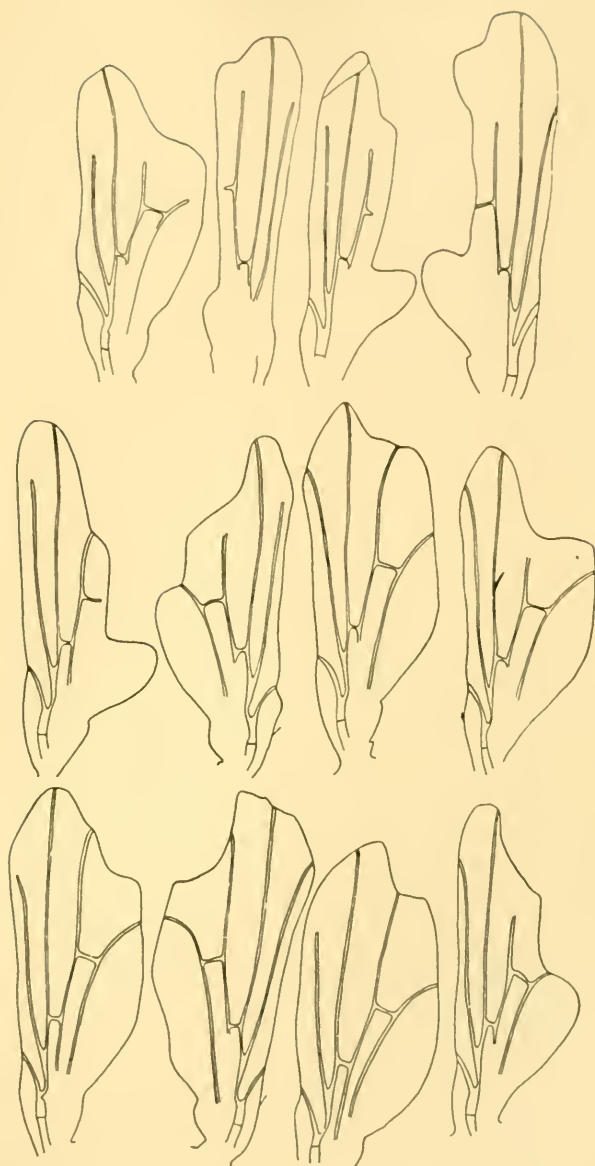


FIG. 3b.

TABLE 3

Phenotype of wings	Temperature shock applied at <i>n</i> th day of larva at 25°									
	5	5½	5½	5¾	6¼	6½	6¾	7	7¼	7¾
Curly.....		8	..	100	100	..	58	80
Spread.....		79	20	4	86	33		
Scalloped.....	16									
Lancet.....				29	..		50	..	4	21
Miniature.....				67	4					

It is important to note that Friesen (1935), in producing phenocopies by X rays, found, as far as I can see, the same sensitive periods. Thus he remarks that the period for spread wings occupies the last larval and first pupal day, whereas scalloping is produced one day earlier. It might be added that very exact determinations of the sensitive period are difficult in this case because the lethality after treatment is so high that mass cultures with a considerable variation in time of development must be used.

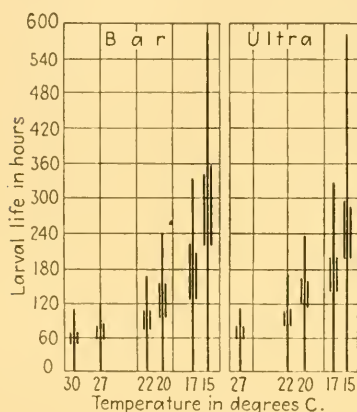


FIG. 4.—The main lines represent the lengths of larval life at the constant temperatures for Bar and Ultrabar in *Drosophila*. The short line to the left of each represents the relative length and position of the temperature-effective period for the females; that to the right of each, the effective period of the males. (From Driver, 1931, *J. Exp. Zool.* 59, Fig. 7.)

Far more exact determination of the sensitive period is possible in the cases of Bar and vestigial, where the described effects are obtained within a normal or almost normal range of temperature. A very considerable amount of work has been done by Zeleny and his school to locate exactly the sensitive period for the temperature effect upon the Bar-eye series in *Drosophila*. Figure 4 represents Driver's (1931) results for Bar and Ultrabar.

In this connection, we are interested only in the fact that sensitive periods exist and that they occupy a definite length in larval

life. Another problem, which is illustrated in the diagram, is whether this period is fixed as a definite stage in development or its place in time is relatively different under different temperature conditions. This special problem will have to be discussed later in connection with the rate concept. In this case, the effective period falls within the third instar, a time at which the eye *Anlage* exists as an imaginal disk; according to Driver, it begins about the time when optic and antennal *Anlagen* are separating from each other, *i.e.*, very early in eye development. It ends, as expected, when actual facets are being formed.

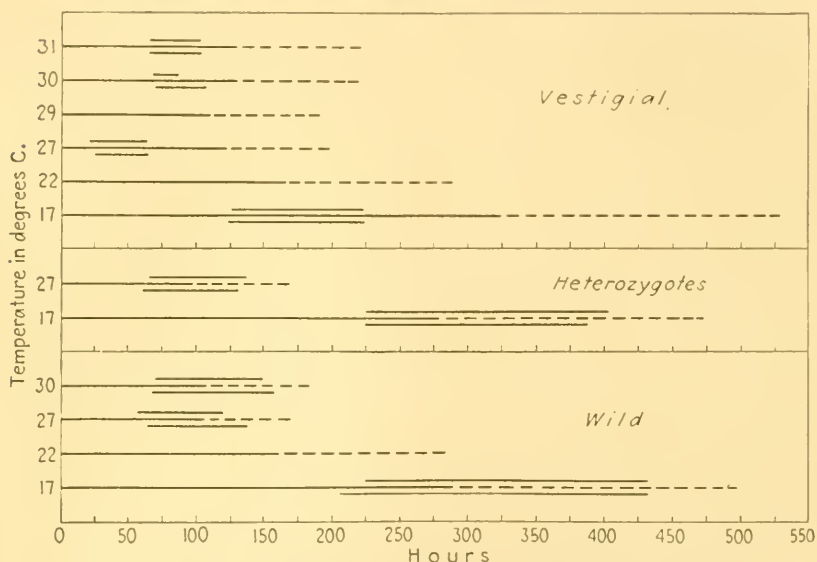


FIG. 5.—Data for the lengths of the developmental periods and the positions and lengths of the temperature-effective period for wing length in *Drosophila*. The long lines represent the earlier developmental periods. The solid portions indicate the larval periods; the broken ones, the pupal periods. The upper short lines represent the temperature-effective periods for wing lengths of the females; the lower lines, those of the males. (From Stanley, 1935, *J. Exp. Zool.* **69**, Fig. 17.)

Another case upon which much work has been done is the vestigial wing. It was reported that the vestigial wing in *Drosophila* could be induced by increase of temperature to change into the phenotype of all the other *vg*-allelomorphs. Stanley (1935) determined the sensitive period for the production of these phenocopies as well as for corresponding effects upon

vg-heterozygotes and also the small wing-lengthening effect upon Wild-type wings. His results are summarized in the graphic representation (Fig. 5).

If these data are compared with the facts known about the development of wing buds, they point out that the important phenocopic effect (30 and 31°) occurs about the time of the third instar when the wing buds are just being formed. This is, indeed, to be expected on the basis of the facts of development of *vg*-wings, which will be reported later. There is, in addition, another very early effect visible at lower temperature, an effect that must have occurred at a time before the wing bud became visible in the larva. In addition, there is a later sensitive period for the heterozygote and the wild type. These discrepancies are caused by a fact, unknown to Stanley, *viz.*, that the effect upon the vestigial wing is something different from the effect upon the Wild-type wing and has nothing whatever to do with growth in length. Only the 30 and 31° experiments upon the *vg*-wing pertain to the phenocopic phenomenon and fix their sensitive period. Harnly's (1936) determinations agree rather well with Stanley's. He fixed the beginning of the sensitive period for all the temperatures that have a phenocopic effect (29 to 31°) at 64 to 68 hr. of larval development, which corresponds to the molt between the second and third instar. The duration of the period was, however, somewhat different at different temperatures.

Let us interpret these facts. It is clear that the process controlling the abnormal development of the wing buds sets in as soon as their *Anlagen* are differentiated. From the facts concerning the development of these mutant wings we shall later derive the conclusion that the different degrees of wing scalloping are dependent upon the time of visible onset of a degenerative process. The sensitive period described here is, then, the period in which this process may be counteracted, perhaps by changing its relative velocity, the effects of which would be the same as a later onset of the process. At first sight, it might seem to be a contradiction that the sensitive period for the phenocopic action in the Wild type occurs much later; the reason is that in the Wild type, the temperature shock starts a process that otherwise would not occur and the amount of which is determined by its onset within a period in which such a process might still be

initiated before the wing structure is completely determined. In the reciprocal effect, however, a process that begins early in development is only slowed down. The sensitive period then covers such a time in development at which the process (early degeneration caused by the *vg*-gene) has not yet gone so far that it could not be slowed down more or less. The reciprocal production of the same phenocopies, at least in part, from the Wild type as well as from the mutant, is then actually the effect of two completely different inductions, *viz.*, in one case, the induction of a process at a definite time and, in the other, the change of rate of an already existing process; both are bound to lead to the same phenotype, because this is determined, given the same process of degeneration, by the product of its rate of progress and the time of onset.

Still more exact data are available for some of the bristle mutations in *Drosophila*. Plunkett (1926) made such determinations for the mutant *Dichaete*, and his student Child (1936) for *scute*. These experiments do not exactly belong to this chapter, as the effect of temperature here is not the production of phenocopies. The *scute* mutant upon which the experiments were performed makes certain bristles on thorax and scutellum disappear. But the amount of suppression of development (or destruction?) of these bristles varies considerably: a certain percentage of individuals shows the absence of one bristle and correspondingly of all the bristles affected. This percentage is influenced by temperature, and there is a temperature-effective or sensitive period involved here. As the same effect may be produced also by genetic modifiers, this case is at best closely related to the case of phenocopies, and the underlying laws are assumed to be the same. Child (1935) found that the temperature effects are more or less specific for each bristle but that the sensitive period is the same for all, *viz.*, situated at a time interval from 75 to 98 per cent of the egg-larval stage. We recall that in our phenocopic experiments the sensitive period for bristles in general (all effects upon bristles) extended also into the pupal stage. Plunkett also found such for the variation of the *Dichaete* type. By still more refined experimentation and statistical treatment of his data, Child was able to calculate the sensitive period for the individual fly—as opposed to the determination for a population—with the following result: This period occupies

not less than 3.8 and not more than 7.5 per cent of the egg-larval period. The sensitive period for any one fly lies between the time when 89.3 per cent and the time when 96.8 per cent of the egg-larval period have been completed. We shall meet these facts again in later chapters.

(In a recent paper, Ives (1935) criticizes the results of Child, because ocellar bristles may be influenced at all times by a temperature of 40 to 41°. But so high a temperature may act very differently, by actual destruction of material.)

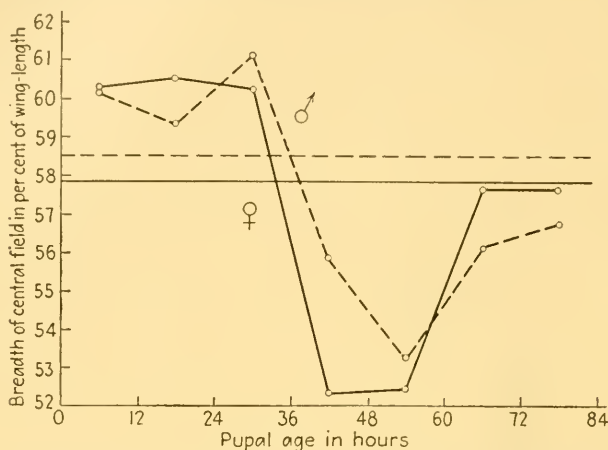


FIG. 6.—Curves for the breadth of the area enclosed by the symmetrical bands in the wing of *Ephestia kuehniella* after temperature action at different stages. The horizontal lines represent the controls. (From Kuehn and Henke, 1936, *Ab. Ges. Wiss. Goettingen*, Fig. 93.)

Finally, one case has to be reported which is of special significance because it will furnish us later with important information regarding the meaning of the phenomenon. In the extended studies upon the wing pattern of the flour moth *Ephestia kuehniella* (Zeller), Kuehn and Henke and their students furnished many facts pertaining to this problem. They found (Kuehn and Henke, 1936) mutants that produce a shift of the two systems of symmetrical bands on the wings toward its center, thus narrowing the central field, called the field of symmetry (see Fig. 7). The same effect may be produced as a phenocopy by treating the pupae at a definite stage with heat shocks (45° for 45 min.), and the sensitive period for this part of the wing pattern was fixed at a time 48 to 60 hr. after pupation at 18°. Figure 6 represents

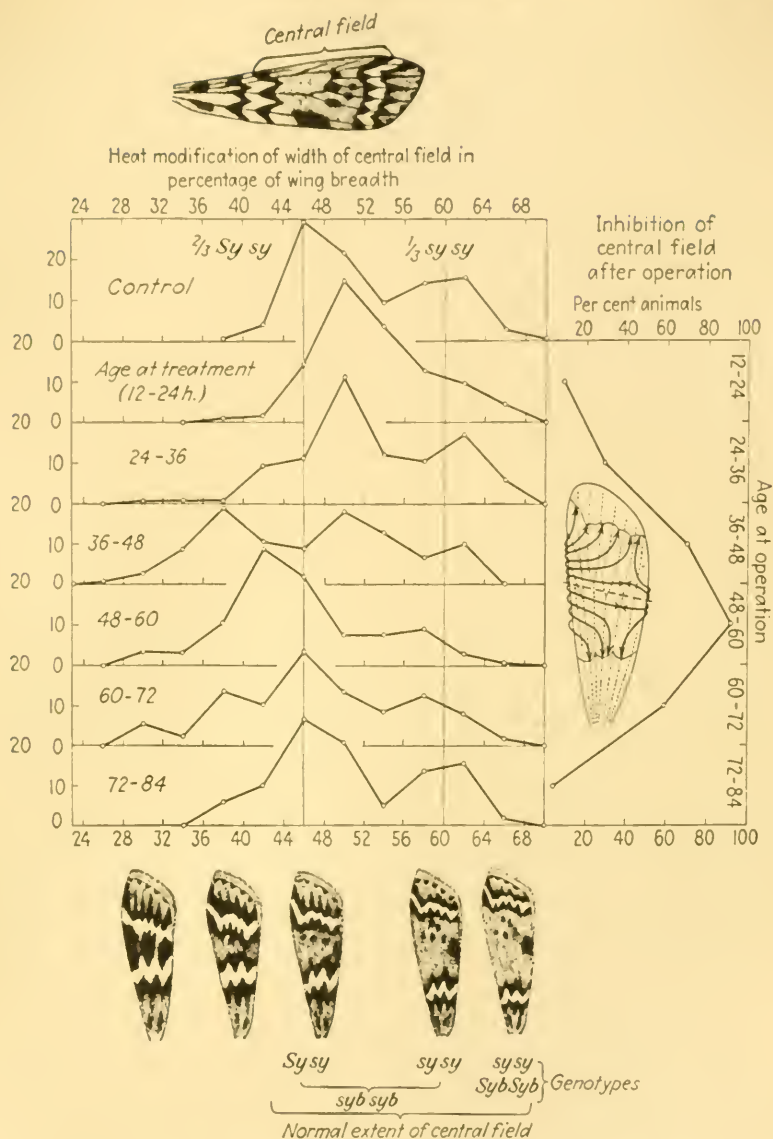


FIG. 7.—Influence of heat shocks of different genes and of thermocauterizing wings upon the breadth of the field of symmetry in the pupae of the flour moth. Left series of curves: influence of heat shocks at different times in a brood segregating into 2 $Sy sy$:1 $sy sy$. Ordinates: percentage of individuals, abscissae: breadth of area in percentage of entire wing. Right-hand curve: frequency of incomplete formation of the same wing area after destruction of parts in percentage of animals operated at different ages. These ages correspond to those for the curves on the left side. Below: type of wings belonging to the different points on the abscissa. The genes of the formulae produce the same effect genetically as otherwise produced by temperature shocks (phenocopies). (From Kuhn and Henke, 1936, *Abh. Ges. Wiss. Göttingen*, Fig. 100.)

a curve of the average diameters of this field on the wing after heat treatment at different times as compared with the untreated controls. A few further details regarding the amount of the reaction may be gained from Fig. 7 to which we shall return later. Similar determinations have been made for other elements of the wing pattern in the same object as well as in *Abraxas grossulariata*, the currant moth. Some of the data will be reported later in the chapter on pattern.



FIG. 8.—Superposition of a heat effect upon the dominigene effect in the heterozygous *vg*-wing in *Drosophila*. Broken curve: amount of scalloping of wings (classes I–V) in the controls, with genetic scalloping produced by the *vg*-dominigenes; average grade for individuals hatching on consecutive days. Full-line curve: The same line treated with temperature shock; on the third day the animals are hatching in which the genetic and the temperature effect are additive. (From Goldschmidt, 1935, *Z. ind. Abstr.* **69**, Fig. 17.)

It is not probable that in higher plants strictly comparable facts will be met with, as developmental mechanics are so different from animals. But Harder (1934) claims that flowers of *Petunia* have a sensitive period in which the pattern may be influenced by temperature and light in a definite way.

D. COMBINATION EFFECT OF GENE AND PHENOCOPY

For our task—to prove that the processes underlying the formation of phenocopies are the same as those set in motion by mutant genes—the following facts are of importance: Goldschmidt (1935a) treated with the method that produces scalloped wings both Wild-type flies and flies that have genetically scalloped wings (*vg*-heterozygotes with dominigenes). The result was that in the latter case the genetic and the phenocopic effect were added, and a more extreme scalloping was produced. Figure 8

represents the result of this experiment. The ordinate indicates the degree of scalloping (classes I to V); the abscissa, the days of hatching; and the dotted curve, the control. On the third day appear the flies that have been treated with heat, and the addition effect becomes visible. Such additional effect is, of course, to be expected only in rather simple cases, its occurrence depending upon the details of the processes involved. Kuehn and Henke (1936) state that in the alteration studied by them, *i.e.*, in the distance apart of the bands on the wing of the flour moth, no additive effect was found.

2. THE PHENOCOPIES AND THE DEVELOPMENT OF MUTANTS

Near the bottom of page 3 are pointed out the limitations set to possible changes in developmental processes by the necessity of their integration into a viable whole. These limitations apply both to mutant changes and to phenocopic changes. We saw that these different causes produce the same end effect, presumably by changing the same developmental processes in an identical way. To understand, then, the type of action of the mutated gene upon development we must be acquainted with the differences between normal and mutant development. The knowledge of this combined with the facts already reported ought to give a first insight into our problem.

A. FACTS OF MUTANT DEVELOPMENT

To test these or other possible views it becomes imperative to know the details of development that distinguish the mutant types from the wild type. Studies of this type have been called by Haecker *phenogenetics*, a term that is not necessary but is sometimes useful. Quite a number of facts are known of various importance for our problem.

A first group includes cases that allow only rather general conclusions. We mention the work of Pernitsch (1913) and Schnakenbek (1921), who studied the development of dark and albinotic axolotls. They found that both contain melanophores and xanthophores and that in the albinotic form these pigment cells have a lower rate of growth and multiplication. Goodrich (1927) found in the fish *Oryzias* a somewhat different behavior: In different color varieties (mutants), the same pigment cells received different quantities of pigment. Such cases, as far as

they go, may be interpreted on the basis of different rates of reaction.

A second group includes cases that are rather complex in detail, because the mutant form exhibits complicated pathological conditions which are difficult to describe in simple terms, although very thorough work has been done. This group contains most of the recent work on mammals and birds. The abnormalities are caused by either recessive or dominant mutant genes, the latter being sometimes lethal in homozygous condition. There is the work of Little and Bagg (1929), Bonnevie (1934), and Plagens (1933) on a recessive mutation produced by X-ray treatment by Little and Bagg. The abnormality is very diversified, affecting many different organs, especially eye and foot. It seems that all these changes are the consequence of a blood extravasate occurring in the neck of embryos 7 to 8 mm. in length (Bonnevie). The blebs move with further development to different places where they obstruct mechanically the processes of development. We may not, in this case, speak properly of changes in development produced by the mutant gene. It actually produces only one effect: In young embryos, fluid from the medullary tube is expelled through the foramen arterius in abnormal quantity, and the blebs thus formed harm the developmental processes wherever they become situated.

In some of the other abnormalities, however, actual developmental processes are changed by the mutant gene. The development of the short-tailed mutation of the mouse, found by Dobrovolskaja (1928) as a dominant mutation, lethal in homozygous state, has been studied by Chesley (1935). (The morphology of the mutant is carefully analyzed by Kobozeff, 1936). The homozygous embryos show, as far as can be determined, normal development up to the somite state. Then a considerable degeneration of tissue sets in, as indicated by the appearance of chromatic granules, in the posterior part of the embryo. This results in the absence of notochord, medulla, and somites and leads to death of the germs ($10\frac{3}{4}$ days after insemination). The facts seem to point out that the degeneration process begins in the primitive streak and therefore affects all the descendant parts (and the induced differentiation) of this region. It is obvious how much this case resembles the case of the vestigial wing in its general features, which will be reported below. In

the heterozygote, the developmental processes involved in producing the short-tailed type are of the same order. But abnormal development, affecting primarily the notochord, begins at a much later stage and therefore affects only (or mostly) the tail. Here, then, the controlling factor is also the different time of onset of the degenerative process, as in the vestigial case.

The number of reports in this field of research is constantly increasing, and the facts appear rather variable, though in general they may be described in a similar way. Here are a few more examples: van Assen (1930) finds that genetic vertebral ankylosis is based upon the occurrence of a fold in early development which causes a shift in the time relations of the developmental processes. David (1932) studied hairlessness in different types and finds it to be caused by very different processes in the different forms. Sometimes development proceeds normally, but at a definite point cysts are formed which destroy the follicle. In still other forms the follicle degenerates. Bonnevie (1936a) extended her studies to the destruction of the labyrinth in Dunn's "shaker-short" mice. In the development of these waltzing mice, the labyrinth develops first normally up to the eleventh day. Only then does abnormal differentiation set in. It is caused by abnormal development of the myelencephalon, combined with a collapse of its ventricle. A consequence is that the auditory vesicle is not innervated and does not continue normal differentiation. We might finally mention in this connection the radium-induced mutant abnormalities of *Antirrhinum*, which Stein (1932-1935) produced. Here, also, a primary tissue destruction of a cancerous type leads to formative changes and abnormalities, though not strictly comparable to the cases in animals.

In the fowl, two comparable abnormalities have been studied. There is the creeper fowl, showing a general achondroplasia of the bones in heterozygous condition, the homozygous mutant being lethal (Landauer and Dunn, 1930b). The morphology and physiology of this mutant have been studied most thoroughly by Landauer in a large series of papers, and we know more about the effects of the creeper gene than about any other comparable case. We shall report the case and other similar ones in another chapter (see page 214).

Another comparable abnormality, caused by a dominant factor (viable when homozygous), is the rumpless fowl, in which the

axial skeleton is shortened and ankylosed in the posterior region (description in Du Toit, 1913; genetics in Dunn, 1926). The details of development have not yet been worked out, but we have already mentioned the fact that this condition has also been produced as a phenocopy by Danforth (1932) (see page 10).

It is rather remarkable that the type of genic effect upon development found in vertebrates may also occur in insects. This means an early effect upon a more generalized developmental process which leads to a number of later consequences. Such facts were described by Speicher (1933) for the development of the eye mutant *Eyeless* in the wasp *Habrobracon*. Here the development proceeds regularly until a late larval stage. At this time, a portion of one pair of imaginal disks fails to invaginate sufficiently to become separated from the larval hypodermis. This leads to a retardation of the development of the dorsal part of the head capsule, resulting in the formation of large lobes in that region. Later, all the elements of the eyes and head appear in normal order but are modified in size and shape by the previous event.

A third group contains work in *Drosophila*, where some decisive facts could be found in the work of Schultz (1935) on eye colors, of Medvedew (1935) on eye form, of Goldschmidt (1935c, 1937) on the mutants of the wing, and of a few others. As the last cases seem to be the simplest for explanation, and as here the parallel with the phenocopies has been established, we shall describe them first.

One of the phenocopies that may be most easily produced both by heat and X rays are scalloped wings. Their type covers exactly the phenotype of the vestigial allelomorphs nicked (*vgⁿⁱ*), notched (*vg^{no}*), up to snapped (*vg^{sn}*). The sensitive period is situated at the end of larval life. A study of the development of the series of *vg*-alleles gave remarkable results (Goldschmidt, 1935c, 1937). Phenotypically a wing of this series appears like a complete wing from which parts have been removed starting at the tip and proceeding toward the base of the wing until only a small stump has been left in the alleles vestigial and No wing (see Fig. 3). (This was known to the first observers but neglected in later work.) The morphology of this series already indicates that the typical subdivision of the wing surface with its veins and spaces between the venation must have occurred in develop-

ment (if not visibly, at least in the form of spatial determination) before the process that results in scalloping begins. Actual development proves that this expectation is literally true. In the scalloped types, almost up to the type of the allele snipped, development of the wing proceeds perfectly normally until pupation, when the wing disk is protruded (evaginated) and expanded to the size and shape of the pupal wing, which secretes its chitinous sheath (Fig. 9). Only then a degeneration, or

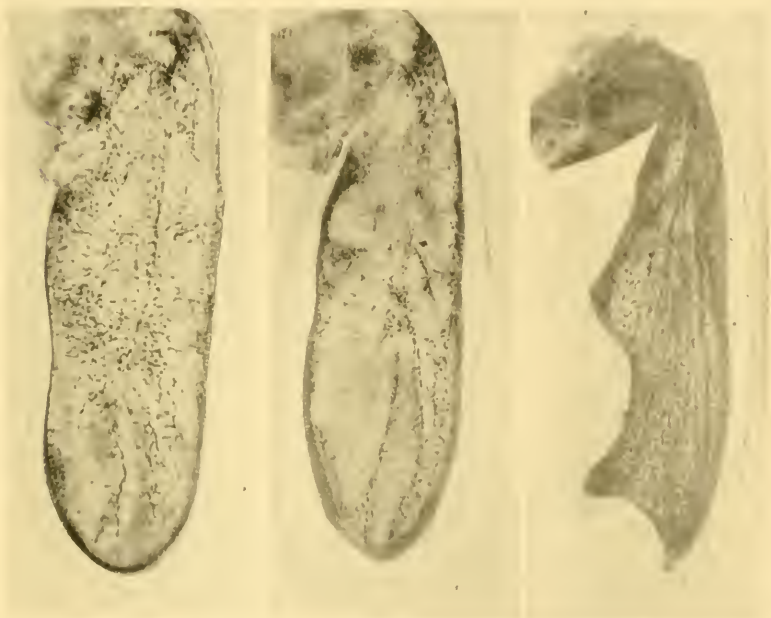


FIG. 9.—Three stages from postpupal development of a *vg vg^{no}* wing in *Drosophila*. The wing is normal at the time of pupation. (From Goldschmidt, 1937, *Univ. of Calif. Publ. Zool.*, pl. 15.)

lysis, of this tissue sets in at the points of later scalloping, and these pathological areas of the wing spread are gradually resorbed to form the nicks and notches (Fig. 9). This resorbing process ends when the details of wing structure are being perfected. It is a general rule that as the process of degeneration sets in earlier and earlier, a more and more extreme scalloping results. In the higher grades, *i.e.*, the phenotypes ragged, antlered, strap, vestigial, and No-wing, the process actually begins in the imaginal disk, and at the time of pupation parts of the wing area have

already been destroyed (Figs. 10 to 14; Goldschmidt, 1935c, 1937; Auerbach, 1936). In the highest types like vestigial, the process must begin in the young imaginal disk. This, however, cannot be demonstrated but has to be extrapolated from the rest of the series.

Similar results have been obtained for a number of other wing mutants like dumpy, cut, pointed, miniature, and beadex, all of



FIG. 10.—Three stages from postpupal development of a *Drosophila* wing heterozygous for *vg/vg^{no}*. At the time of pupation the wing is already incomplete. (From Goldschmidt, 1937, *Univ. of Calif. Publ. Zool.*, pl. 16.)

which show normal development up to a certain point, followed by an onset of degeneration of tissue at typical points (different in different cases) or by a slowing up of certain growth phenomena of the already differentiated wing. There are, however, also cases where obviously a different growth rate is present from the beginning (mutant expanded).

These facts, then, show that the mutant gene makes something necessary for normal differentiation to be absent or below the necessary threshold after a certain time in development (or, vice versa, produces something acting as a lytic substance above a



FIG. 11.—Three stages of development of a straplike *Drosophila* wing. Considerable abnormality already at time of pupation. (From Goldschmidt, 1937, *Univ. of Calif. Publ. Zool.*, pl. 17.)

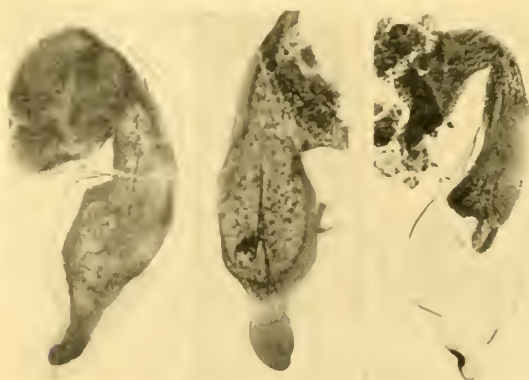


FIG. 12.—Development of the *rg*-wing in *Drosophila* after pupation. Most of the wing area destroyed before and much after pupation. (From Goldschmidt, 1935, *Biol. Centrbl.* 55, Figs. 47-54.)

certain threshold); and furthermore, that the time of visible onset of this gene-controlled deficiency is a simple function within the increasing series of allelomorphs. Without going into further details here, these facts indicate that here, again, processes of definite velocity are controlled by the different mutant genes and, also, processes having velocities of different but typical rate in series of alleles with increasing phenotypical effect.

It is encouraging that Harnly (1936), whose studies on the sensitive period of the vestigial series have been mentioned, derived from his facts (which have to be restated in different terms, as the development of the *vg*-wing was not yet known to him) a very similar interpretation. He concludes (1) that there is a definite pattern of wing development in time (in a later chapter, we shall see that it is not pattern of development but pattern of a determination stream); (2) that the degree of expression is dependent upon the duration and rate of processes occurring in the larval period of the vestigial genotype; (3) that mutations at the vestigial locus apparently affect the duration and rate of these developmental processes.

A considerable amount of work has been done on the eye mutants of *Drosophila*, though the results are far from being complete. The eyes are formed from an imaginal disk which separates from the pharynx as the so-called cephalic complex after 8 to 16 hr. of larval development (total 206 hr. at 27°C.). Between 36 and 48 hr. at 27° this complex is divided into optic and antennal buds, the former now being the eye disk proper. This grows and differentiates until it is finished—except for the pigment—at about 84 hr.

The mutants of eye form have been studied by Chen (1929), Krafka (1924), Johannsen (1924), and others. The most complete account thus far available is for the mutants conditioning decreasing size of the eyes *glass*², *eyeless*², *Lobe*^c, studied by Medvedew (1935). This author finds that the differences between these types (including the variability and asymmetry of *eyeless*) are already visible at 24 hr. (27°C.), though they are rather small. From this time on, growth proceeds perfectly parallel in regard to percentual increase. Figure 13 shows the curve of growth for these four types, age of larva plotted against logarithms of disk size. The initial differences as well as the parallel growth rate is visible. The drop of the curves at 48 hr.

indicates that up to this time the cephalic complex was measured, and later the eye disk alone. The actual differences are then determined very early in development. Unfortunately, nothing at all is known as to how these differences originate—whether fewer cell divisions take place or an *Anlage* of normal size is second-

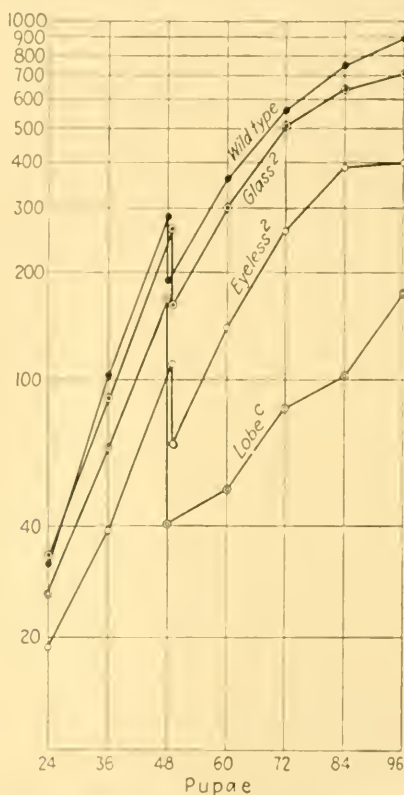


FIG. 13.—The logarithmic growth curves of the imaginal eye disks of Wild-type, glass, eyeless, and Lobe larvae (between 36 and 48 hr. the cephalic complex separates the eye disk proper). (From Medvedev, 1935, *Z. ind. Abstl.* 70, Fig. 3.)

arily reduced. Thus at present the only conclusion to be drawn is that genes are involved which control early processes of differentiation. It seems that the story is a different one for the Bar-eye mutants of *Drosophila*. According to Chen, the youngest stages of the Bar eye have the same size as those of the Full eye, and only later do the size differences appear. No details are yet known; but certain experimental facts (see page 76)

point to the possibility that in this case a phenomenon may occur similar to that observed in the vestigial case, *viz.*, a secondary though rather early destruction of already formed eye material.

A few facts, published recently by Wolsky and Huxley (1936), actually point in this direction, though they are in no way conclusive as yet. In the Bar eye, there are small areas adjacent anteriorly and sometimes posteriorly to the region of faceted ommatidia in which no facets are found, though the pigment is present. The authors found that in this region the retinula cells and the dioptric apparatus are lacking and only the pigment-bearing accessory cells are present. This fact may or may not permit conclusions upon the formation of the Bar eye.

A case of a different type is the development of the eye-color mutant characters of *Drosophila*. Schultz (1935) has made a special study of the eye pigments of *Drosophila*. It was known from the work of Johannsen (1924) that the normal Wild eye contains in its pigment cells deep red, orange, and yellow granules. These are contained within the so-called primary and secondary cells and beneath the basal membrane (see Hertweck, 1931). The yellow granules are rather rare and occur only in the primary cells. These pigments appear first about 50 hr. after pupation (25°C.), first around the basal membrane, then in the secondary, and last in the primary cells. The general color at this time is tan. At about 80 hr. the color changes to red, again in the same centrifugal seriation, still leaving some yellow granules in the primary cells.

Both the red and yellow pigments are water soluble and may be separated chemically, and the red pigment can be oxydized into the yellow one. Reciprocally, the tan pigment of the early pupa may be reduced to red by action of H_2S . This means that only one pigment, in different states of reduction, is present. The eye-color mutants, of which so many have been described, are of two main types. One group shows bright reddish colors. These eyes contain dense yellow or orange pigment in the cells and little pigment below the basal membrane. The second group of more brown shades contains hardly any pigment in the primary cells; red and yellow or only yellow granules in the secondaries. There is also an intermediate pinkish group of the pattern of the first group but with red and yellow granules. Furthermore, in

addition to the stage of oxidation, the pattern of pigment distribution is involved as well as the amount of the two main pigments present. Within the general frame of this grouping, innumerable variations may be found in regard to both total amount and relative concentrations of the pigment.

The study of development reveals that there is a characteristic feature regarding the development of these colors. The following table taken from Schultz shows the percentages of pupal development completed at the time when pigment first appears for different eye-color types.

TABLE 4
(From Schultz)

Type of eye color	Percentage of pupal development complete at	
	First appearance of color	Darkening of bristles
Group I:		
apricot.....	53	81
brown.....	53	83
carnation.....	48	79
clot.....	52	74
prune.....	49	76
purple.....	51	71
sepia.....	55	79
wild.....	55	83
Group II:		
garnet.....	56	77
light.....	57	82
peach.....	55	74
ruby.....	53	74
Group III:		
cardinal.....	63	74
cinnabar.....	71	77
scarlet.....	68	77
vermilion.....	71	75

There is a first group behaving very much like the Wild type, and a second similar one. But with the colors of the third group the pigment appears only at the time when the Wild type changes from tan to red (coinciding with darkening of bristles). There is, then, a typical difference in the onset of pigment formation.

As far as this work goes, it proves that the embryological difference between the different mutants consists in differences (1) in time of onset of the process of pigmentation; (2) in the amount (or rate?) of oxidation and reduction; and (3) in the pattern of deposition of pigment (probably also in the size of the granules). Such a combination of reactions of different rate as found here had actually been postulated by Goldschmidt (1920*b*, 1927*c*) as a basis for the explanation of this and similar cases.

As a supplement to the results on the *Drosophila* eye, the facts that Wolsky and Huxley (1934, 1936), described for the development of eye mutants in *Gammarus* are of importance. There are mutants in eye structure in which the retinula is absent or reduced to scattered cells, the crystalline cones are defective, and the eye is composed mostly of hypertrophied connective tissue. Furthermore, the optic tract is affected (which is also the case in the *Drosophila* eye mutants). The development of these eyes is abnormal from the outset: the retinula cells are deficient in number, do not form regular groups, and later degenerate. Simultaneously the interstitial cells hypertrophy. The centrifugal differentiation of the optic tract with its three ganglia is delayed and inhibited. The adult tract then resembles a developmental stage of the normal eye. As far as this description goes it seems that this development is comparable to the one of the vestigial mutant; very early probably the *Anlage* is normal, but early in development degeneration sets in, beginning in the distal region of the organ. From these facts we may expect that a histological study of the early stages of the *Drosophila* eye mutants might reveal similar conditions and not simply a retarded growth.

Some of the phases of the process of pigmentation as dependent upon mutant genes seem to be more easily understood in birds. The pigmentation of the feather and the general basis of feather colors has been the subject of numerous researches of which we mention especially the school of Haecker, because they worked with genetical ends in mind (Haecker, 1918, 1925; Goernitz, 1923; Kniesche, 1914; Spoettel, 1914). In a general way, the different colors are produced by a combination of (1) Eumelanins = dark relatively insoluble pigments; (2) pheomelanins = yellow

or brown soluble pigments both formed by oxidation of dioxyphenylalanin (Dopa) through an oxidase according to Bloch; they are always deposited in the form of pigment granules of different shapes; (3) The yellow lipochromes, derived from carotins, stain the horny feather cells in solution. (4) With these pigments the structural colors act to produce the phenotype. (a) The walls of the external cortical cells of the feather rami contain fine air tubes which produce the blue color of cloudy media. The blue is enhanced by a black background; the addition of lipochrome color to both produces green; (b) If the superficial layer of rami and radii splits into fine scales, another optic effect is produced responsible for the bluish grey of pigeons, etc. It is again blued by a background of black; (c) An iridescent effect is produced if the radii containing melanin are broadened (Rensch, 1925), and the thin horny scales above them act as thin lamellae. A study of these colors as controlled by Mendelian genes in the buderigar (*Melopsittacus undulatus*) has been made by Steiner (1932). In the development of the feather germ, pigment appears first in the so-called dendritic cells, *i.e.*, branched melanophores, which are situated at the basis of the future branches which are formed as rows of cylindrical cells. In the green race, which contains dark pigment (besides lipochrome and the blue effect), simultaneously the cylindrical cells of the young rami produce melanin. In another race with gray wings, which contains less melanin, the dendritic cells contain more melanin, and the cylinder cells less; and in a yellow or white race, still more pigment is contained in the dendritic cells, and none in the cylinder cells. These dendritic cells, however, do not enter the formation of the feather but are later removed when the young feather breaks through. In the three cases, then, the same amount of pigment is formed but is distributed differently upon the feather cells and the impermanent dendritic cells. This may mean either of two things: (1) The chromogen is formed in the dendritic cells and diffuses from these to the feather cells. The time at which oxidase is released means pigment formation and the end of diffusion. Earlier release, then, means less pigment for the cylindric cells. (2) The dendritic cells may reach a threshold for pigment formation from chromogen at an earlier time and thus absorb more of the available chromogen. These

two interpretations, proposed by Steiner, fall completely in line with all the other facts discussed in this chapter, *viz.*, a genic action through the regulation of the velocity of one or another process.

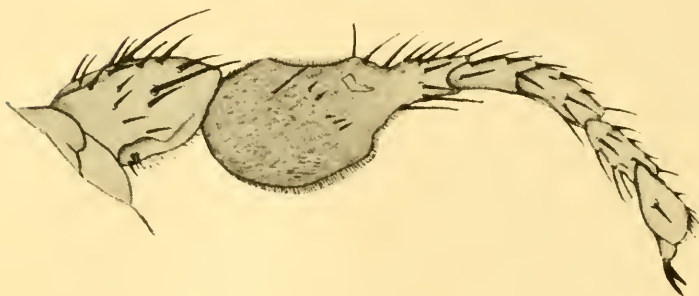
In the case of blue forms, the lipochrome is involved only in so far as it is completely absent. If this deficiency is combined with low melanin formation (as in yellows), the result is white. The olive colors, however, depend upon a change in the arrangement of the air-filled tubules in the medullar cells; the respective gene has therefore a morphogenetic effect. (Regarding different degrees of lipochromes, Duncker has derived physiological explanations from his genetic work on canaries and budgerigars. But his analysis has not been substantiated by chemical or morphogenetic facts.)

As a rather remarkable case might be mentioned the development of the mutant *aristapedia* of *Drosophila*, according to Balkashina (1929). This mutant belongs to the group of homoeotic changes, where one organ is transformed into a homologous one. In this case, the bristle on the antenna, called *arista*, is transformed into a tarsus by a simple recessive mutation (Fig. 14). In normal flies, segmentation of the antenna in the imaginal disk begins in a larva of 4 to 4½ days (25°) and ends in the young pupa. In an *aristapedia* fly, however, segmentation begins in a 2-day-old larva, when the segmentation of the leg *Anlage* also takes place. This segmentation is at once of the leg type and continues thus. We shall return later to this remarkable case and point out here only that the immense morphogenetic effect seems to be produced by nothing but an earlier incidence of a morphogenetic process.

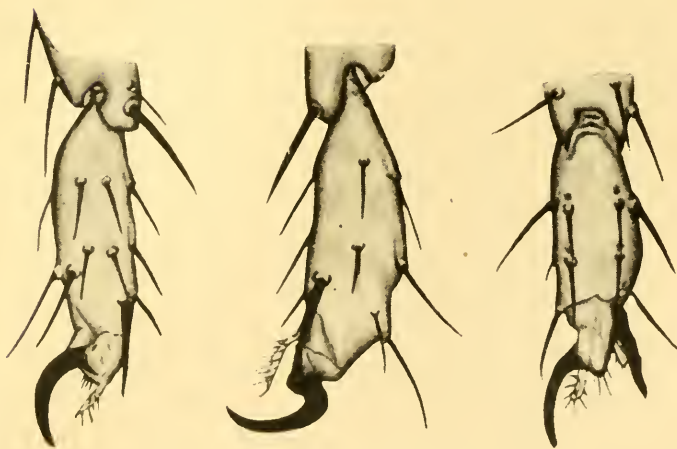
The cases thus far considered all involve changes in developmental rates. The actual processes involved are not clearly indicated, although it is possible to draw inferences about them. There are also cases of a much simpler type, some of which will be reported in the chapter on rate-controlling genes. Here only two of them may be mentioned because they illustrate two simple types of mutant development. Gabritschevsky and Bridges (1928) studied the development of the giant race of *Drosophila* and found that it is indistinguishable from normal development up to the time at which pupation ought to occur. The giant larva then continues to grow a few more days before it



a



b



c

FIG. 14.—a, antennae of normal fly; b, antenna of aristapedia; c, last joint of aristapedia compared with normal tarsus (right). (From Balkaschina, 1929, *Arch. Entwicklmech.* **115**, Figs. 1, 6, 7.)

pupates. As we know now from the work of Buddenbrock (1928-1931) and Wigglesworth (1934-1935) that pupation is controlled by hormones, this might mean that the mutant gene causes this hormone to be produced at an abnormally late time. A case that might be called the reciprocal of this has been studied by Dobzhansky and Duncan (1933). In the *Drosophila* mutant chubby (a larval shape), the abnormal growth ratio, leading to the changed proportions of the larval body, has already occurred during the embryonic stage and is completed when the young larva hatches. But this is an example of rate genes which will be treated in a later chapter.

As there is not much botanical material available regarding the development of mutant characters, two investigations might be mentioned here which show that probably the same type of processes will be frequently found to be involved. Anderson and Abbe (1933) found that the considerable and manifold morphological differences between *Aquilegia vulgaris* and the mutant *compacta* are altogether the consequence of an earlier onset of secondary thickening of the cell walls in the development of the stems.

A somewhat more complicated and therefore less clear case, the development of ear form in wheat, has been studied by Philipchenko (1929). The complication is derived from the fact that quite a number of genes are involved in controlling the form so that it is not actually a difference in regard to the action of one mutant gene that has been studied, though an effort was made to isolate individual actions. The results may be summarized thus: there is a definite general pattern of development of the ear, of its growth and differentiation of parts, in all hexaploid wheats. The genes for form of the ear do not affect this general development but act upon it in different ways of inhibition. There is inhibition of differentiation of the spikelets (genes e_1 and p) and inhibition of growth of ear (gene C) and its parts (gene N). Some of these genes act relatively early: at the beginning of the general differentiation of the ear (e_1p) or about midway (C_1N). But the majority of genes produce such changes only toward the end of development.

The same general type of development occurs also in the tetraploid species of *Triticum* but is different in *T. monococcum* and in *Secale*, a point that is of more interest, however, for problems of phylogeny.

B. MUTANT CHARACTER AND DEVELOPMENTAL STAGE

In the case of the *Gammarus* eye, we have encountered the fact that the adult mutant type shows a condition that may also be described as the fixation of a definite developmental stage. This is clearly an important point for an understanding of the action of the gene, as was emphasized by Goldschmidt in the first stages of his work on intersexuality (1917*b*, 1920*c*) and therefore some more facts ought to be mentioned at this point of the analysis.

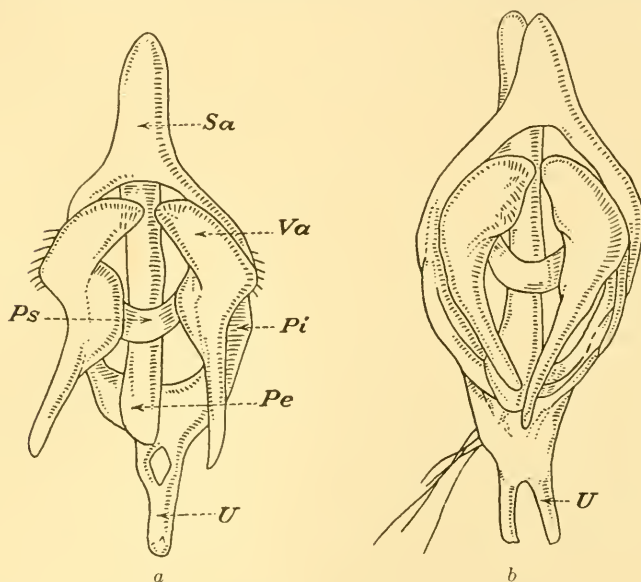


FIG. 15.—*a*, male genital armature of *Lymantria dispar*. *Pe* penis, *Ps* sheath of penis, *Ri* segmental ring, *Sa* Saccus, *U* uncus, *Va* valva; *b*, the same in low intersexuality, also after temperature treatment; uncus double. (From Goldschmidt, 1920.)

A very frequent type of abnormality is the *Hemmungsmissbildung*. This means that development has simply stopped at a definite stage with the result that an embryonic condition is carried into the adult stage, with such modifications, of course, as are impressed upon the organ by the further development of the whole. These abnormalities very frequently involve incomplete concrescence of embryonic parts, like harelip, hypospadia, cleft eye, and cleft palate. Many such types are also caused by

mutant genes, the effect of which must be to stop further differentiation at definite points and at a definite time or to retard it so that it cannot be completed. The following example shows such a process actually both in the form of a genetic effect and in the form of a phenocopy (Fig. 15): In low-grade male intersexes of *Lymantria dispar*, the part of the genital armature called *uncus* becomes paired, a transition from the unpaired male condition to the paired female homologous structure (labia), and this intermediate condition is caused genetically by a definite genic combination. Kosminsky (1909, 1924, 1927) and later Goldschmidt (1922*b*) showed that this same condition may be produced by action of cold upon young male pupae, and Bobroff produced the same effect by X rays (1930). Kosminsky further showed that the *uncus* in the male is first laid down as a paired *Anlage* which later coneresces; the treatment at the proper time prevents conerescence just as the intersexual genetic condition does. Another case of this type is the eye abnormality called *coloboma*, consisting of incomplete coalescence of the eye bulb. This occurs as an inherited anomaly and may also be produced in rabbits by feeding turpentine to the pregnant mother.

The analysis of this and similar cases, a considerable number of which are found in the different organs in case of intersexuality, furnished many facts, which demonstrate that an embryonic or developmental stage of an organ may become perpetuated in the adult as a consequence of definite genetic conditions which generally are of the same type as a mutation (here a mutant condition of sex genes). We shall therefore not be surprised to find that frequently a mutant type is identical with a developmental stage of the Wild type. As examples, I mention the work of Tammes (1934). She found that in *Linum usitatissimum*, a number of genotypes may be isolated that are distinguished by different grades of coloring of the seeds, in fact different steps of the spreading of color around the seed. A study of the development of coloration in normal seeds showed that all the conditions found in the different mutant genotypes reappear as stages of normal development in which color first appears at the pointed end of the seeds and spreads along the edge to the broad end of the seed. Both faces of the seed remain light. Then this light spot is more and more restricted until the whole is self-colored. Tammes also realized that the explanation of this

case is to be found by applying the concept of rates of deposition of pigment, which are changed by the mutant genes or stopped before completion.

Another but probably somewhat more complicated case is furnished by the different hereditary abnormalities of the human hand, *e.g.*, brachyphalangy. In normal human development, the second row of phalanges is formed in the third month, but its development is not finished until after that of the rest of the bones of the hand. In brachyphalangy, they do not appear until later and attain therefore only an embryonic condition if they continue development at all. (For facts see Pol, 1921; Mohr and Wriedt, 1918.) These cases will be cited in a later chapter on rate mutations.

A complete survey of mutant types of animals and plants might furnish innumerable such examples, which have been described as abnormalities by arrest of development. One such instance is to be found in the anomalies of the human eye as analyzed by Waardenburg (1930). He analyzed thoroughly a case of hereditary ptosis combined with different abnormalities of the eyelids and lachrymal apparatus. By careful comparison with the embryological facts, he came to the conclusion that in this as well as in other hereditary abnormalities of the eye an embryonic condition has been preserved as the result of a gene-controlled disturbance in the interplay of developmental reactions, of course followed by such adjustments as are forced upon the organ by the further development of neighboring parts. (We might point out here also the phylogenetic significance of such facts. Waardenburg mentions the theory of Boek that human morphology is a "fetalization" of the morphology of apes.) I have quoted in this connection in a former book the fact that the rudimentary wings of carabids represent the stage of pupal wings. Such examples could be multiplied indefinitely.

There can then be no doubt that the action of mutant genes is very frequently of this type. In dynamic terms, it might be described as an insufficient production of substances needed for growth and differentiation, an insufficiency that reaches at a definite point of development a subliminal condition instead of coming up to the necessary threshold value. The basis for such a description of the underlying process is derived from the existence of series of such effects with different times of onset of the

process dependent upon a series of multiple alleles. This, however, anticipates the discussions of a following chapter.

C. LETHALITY

It is one of the elementary facts of genetics that mutants with rather large somatic effects tend to be lethal. In terms of gene action, this would mean that the change in developmental processes produced by the mutant gene is of such a magnitude that the proper coordination and integration of the different but simultaneous processes are put out of gear. The study of the phenocopies together with certain genetic facts brings these facts into line with the general concept of gene action.

In Goldschmidt's work on the vestigial wing in *Drosophila*, it was found that the sensitive period for scalloping of the wings occurred a short time before pupation. It was further found that the maximal phenocopic effect produced at this time by heat treatment corresponded to the effect of the alleles notched to snipped or to grade V to VI, if the amount of scalloping is divided into 10 classes with nicked as class I and vestigial as X. The study of development of flies with different allelomorphs further showed that no visible degeneration of wing area has taken place at the time of pupation, if the maximal final result is class VI of scalloping. This means that the mutant genes up to snipped will act in such a way that the visible effect does not occur before the sensitive period and presumably that their action occurs actually within this sensitive period. We know, furthermore, that the higher alleles produce a similar visible effect before this period and the highest alleles even in early larval stages. We might infer from this that other sensitive periods exist in which definite gene action takes place, maybe before each molt, and the work of Harnly points to such a period at the molt from the second to the third instar.

It is now known that the imaginal disk which produces the wing also contains the material for the thorax segment and that this material becomes separated from the wing material only in the course of development. A degeneration of tissue produced by the *vg*-allelomorphs will therefore affect the development of the thorax segment also, if the action takes place very early. It seems that the onset of the action of the *vg*-gene occurs just near this point in development; in some lines of *vg*, individuals with a

half thorax are exceptionally frequent. (Occasionally they occur also in long-winged stock.) Such animals are at the limit of viability; if one side only is affected, they may survive; both sides affected would be fatal.

Here, then, we are facing the point where a gene effect begins to be lethal, and we see why: The action of the gene comes into effect so early in development that a group of cells is affected that still has a rather unrestricted prospective potency, which would be restricted or segregated only in later development. The effect of the gene-controlled process therefore influences a whole group of processes of differentiation instead of a single one in case of an effect at a later stage at which the material is already subdivided in regard to determination. Therefore these early effects tend to be lethal. In the *vg*-series, this is especially clear: the highest alleles of the No-wing type are lethal in the homozygous condition. Probably comparable cases are more frequent than is at present known.

The same facts are found in the cases of mammalian abnormalities which were described on page 24. Here it was possible, at least in one case, to compare homozygous and heterozygous action. It was clear that the lethality of the homozygous effect was a consequence of the early action of the gene in destroying *Anlagen* of a considerable prospective potency, involving whole organ systems.

The facts here described are of considerable general importance; they show that the action of mutant genes may be confined to definite periods of development; this would not imply necessarily that these genes are inactive otherwise. It would probably mean that the tissues were in a condition to react only at definite moments. And it seems, furthermore, that these moments of susceptibility are those in which processes of determination take place, *i.e.*, of subdivision or segregation of potencies. If further work should prove this to be a rule, an important link between genetics and development would have been established.

We do not mean to express the opinion that all lethal actions are of this type. Certainly lethal gene actions may also occur if some physiological process of vital importance is damaged or completely inhibited. The best examples of this are the chlorotic mutants of plants, which cannot survive for lack of chlorophyll. But shoots of this constitution may grow upon a green stalk.

Similarly, merogonic tissue in *Amphibia* dies, except when grafted or grown upon a normal host (Baltzer, 1933). The same applies to haploid *Drosophila* tissue (Bridges, 1930). Otherwise doomed tissues of a lethal brachyuric mouse may be grown in vitro (Ephrussi, 1935), and lethal deficiencies may exist as mosaic spots (Ephrussi, 1934). All these cases show a physiological damage produced by mutant genes or lack of chromosome material, which spreads within the tissues and may therefore be counteracted by the presence of normal tissue. These facts do not, then, belong to the problems discussed in this chapter. The same applies to genic interactions which might produce lethal effects by lack of some coordination. Kosswig (1929b) and also Goodrich (1935) showed that in hybrids of the fishes *Platyoeilus* and *Xiphophorus* the pigment cells produce such an excess of pigment that actually fatal melanotic tumors occur. A similar effect in early development would, of course, also be lethal.

D. PRELIMINARY CONCLUSIONS

The study of the phenocopies, the sensitive periods, and the development of mutants already permits some conclusions which have been partly anticipated at different points of the description. Two different sets of facts are pertinent. First, we consider the cases where the phenotypic expression of a mutant trait is a function of temperature within the physiological limits of adaptation to temperatures (in *Drosophila* *ca.* 16 to 30°). In these cases, *e.g.*, Bar eye in *Drosophila*, the effect follows the well-known rules for temperature action upon life processes. In this connection, it is of no importance whether this effect is described in terms of the Van't Hoff or the Arrhenius or any other formula. The fact is decisive that the effect is of the same type as observed in certain chemical reactions, without any additional features, roughly described in the terms of the Van't Hoff formula as an increase of two to three times for 10° rise of temperature within the physiological temperature zone. In these cases, some of the multiple alleles of the mutant produce an effect at normal temperature that is situated within the range of the experimentally varied effect at different temperatures. If, then, the effect of raising the temperature is to increase the velocity of some reactions or processes, it seems that the mutant (multiple) allelomorph

exercises the same effect. Zeleny (1923) who first analyzed such cases, as reported, summarized the results with the words: ". . . demonstration . . . of the fact that the gene Ultrabar has the same type of reaction as a temperature difference. It is possible to state the effectiveness of particular germinal factors in terms of corresponding effects of temperature." Rates of reaction were not mentioned in this connection, as Goldschmidt had already done in 1920*b* in trying to explain the phenocopic phenomenon (as well as the general action of genes), but no other way seems available to describe these temperature effects and simultaneously the effect of the mutant alleles. Such was done by Goldschmidt (1927*c*) in regard to the facts found by Zeleny; and in his last reference to his work, Zeleny (1933) himself writes:

Since the circumstances connected with the production of the Bar mutants make it possible to formulate a theory of difference between the genes of the series in terms of structural change, quantitative in some cases, and since the resulting somatic effects may be measured in terms of temperature effect upon an individual with unchanged genes, it seems worth while to postulate, for purposes of experimental test, theories of gene action in terms of relative rates of the physiological effects they produce.

The second type of experiments did not use external agencies within the range of physiological conditions but actual shocks, which proved fatal if prolonged. It is characteristic for this set of experiments that similar effects are produced by different methods. Thus heat, frost, X rays, narcotics, CO₂ (the latter in von Linden's experiments on butterflies) produced similar effects. True, they were not entirely identical. Thus Friesen's X-ray phenocopies in *Drosophila* were not wholly—though in part—identical with those produced by heat; in the experiments of Kuehn and his pupils, heat and frost had somewhat different effects on certain parts of the wing pattern of the flour moth. But in a general way, the same effect was produced. From such facts, the early experimenters upon the butterfly wing, who were not yet interested in genetical problems, concluded that the effect was produced by reducing differentially the velocity of some of the processes involved in the production of the normal phenotype (von Linden, 1904). Goldschmidt (1920*b*) when analyzing the typical effects of temperature upon the lepidopteran wing went a step further: He stated that evidently

different processes with a different temperature coefficient were involved which therefore were influenced differentially (speeded or slowed) by the experimental temperature. The same interpretation of the facts was later used by Zeleny (1923, 1933) and by Harnly (1935). I think, however, that this interpretation fits only the results of experiments within the range of physiological temperatures. Outside this range, temperature shocks will act always by differentially slowing down some processes.

All the recent investigations bear out the essential correctness of such a conclusion. Applied to the mutant gene, which acts with identical effect as those shocks, this means that the mutant gene acts by changing the rate of definite developmental reactions or processes. Based on this conclusion, the further inference is drawn that each gene acts through the control of rates of reaction (Goldschmidt, 1917*b*, *d*, 1920*b*, 1927*c*).

It seems that this conclusion, which the author has always been inclined to consider the basic insight into the action of the gene and which originally was derived from experimental facts reviewed on page 52, is being more and more verified in recent work. Many of the authors who have performed experiments bearing on this question have now accepted this viewpoint: Plunkett and Child, after a study of bristles in *Drosophila*; Zeleny, in his experimentation on Bar eye; Harnly, who studied vestigial wing; Dunn, after a study of minutes in *Drosophila*; Huxley and Ford, studying eyes of *Gammarus*; and many others, analyzing different types of cases (Wright, Honing, Tammes, Sinnott, etc.). We shall refer to these facts at their proper place in our discussion.

E. SOME PERTINENT FACTS FROM EXPERIMENTAL EMBRYOLOGY

At this point, some facts ought to be mentioned which in a general way supplement the conclusions thus far derived. We have already described Danforth's experiments, producing the rumpless type of fowl as a phenocopy by experimenting upon the embryo. In this case, the type produced corresponded to a well-known type produced by a mutant gene. Many similar cases are known, in which the treatment produces definite abnormalities, definite types of monsters, though not exactly of the same type as known mutants.

Many experiments have been performed upon lower vertebrates which resulted in the production of typical monsters. In fact,

the whole set of recent experimentation upon amphibia might be quoted. But what is important for our present discussion is the production of monsters identical with those found in nature and of essentially the same type as those caused by mutant genes. We shall therefore not report upon experiments of transplantation or removal of embryonic parts, which lead to monstrosities, as these are not comparable to the effect of gene action, though analyzing directly the localization of decisive materials (Lewis, Spemann, Harrison, Holtfreter, etc.). Stockard (1913) was the first to produce typical monsters, especially cyclopia, by the action of magnesium salts upon early embryonic stages of *Fundulus*. Other authors as well as Stockard himself found later that the same effect could be brought about by many agencies such as anesthetics (McClendon), acetone and butyric acid (Werber, 1916), low temperature (Kellicott, 1916; Stockard, 1913), ultraviolet rays (Hinrichs, 1925), and X-rays (Little and Bagg, 1929). This reminds us of the early experiments with the butterfly wing, where about the same agencies proved effective in changing the pattern. And the comparison is still closer if we add that in the experiments just reported there is also a sensitive period, *viz.*, from the fertilized egg up to the stage of neurula. It is therefore not surprising to see that Stockard (1921) derived the same explanation, *viz.*, an action of all these factors upon the speed of certain developmental processes. He states that all methods employed have more or less the same effect, without apparent specificity. (Notice the parallelism with the phenocopies.) The reason is that all these methods primarily slow up the differentiation of the embryo. The state at which this happens decides which type of monster will be produced. Not all stages of development react, however, in the same way; *e.g.*, the treatment of fish eggs before gastrulation produces mostly double monsters; after gastrulation, abnormalities of the eye. Other periods of development seem to be inaccessible to such experiments. From this it follows that there are definite sensitive periods for this type of treatment, and they are found near the period of visible origin of the organ in question. Stockard thinks that the actual basis of the phenomenon of sensitive periods is to be found in the assumption that the organ at this time grows and differentiates faster than the others. A retardation at this moment, therefore, has a differential effect. If we

leave the last specific consideration out of account, it is obvious that these facts and their interpretation fall completely in line with the results of the analysis of the phenocopies.

There is another interpretation of these results by Child (1925) and his student Hinrichs (1925) which seems at first sight to be different. According to Child, pattern is determined by a metabolic gradient which begins with a dominating high level

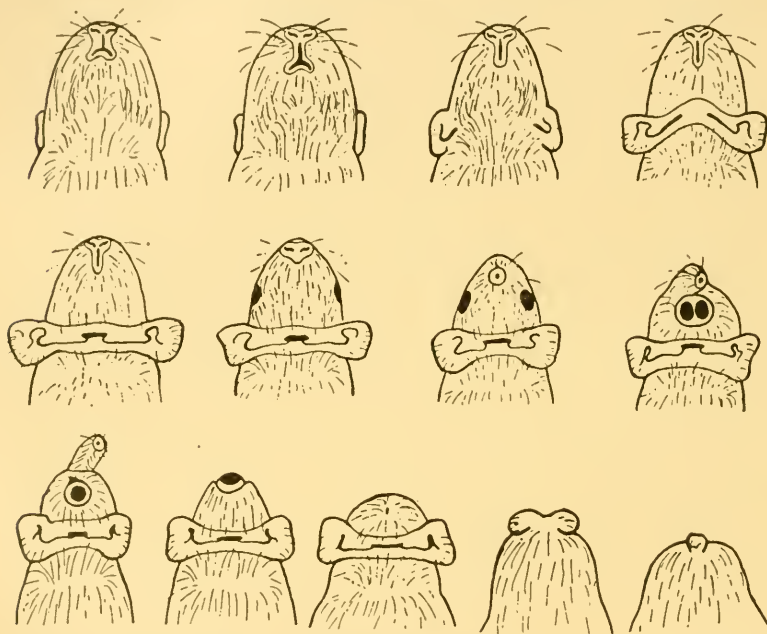


FIG. 16.—Semidiagrammatic representation of the main series of grades of otocephaly in the guinea pig. (From Wright, 1934, *Genet.* **19**, Fig. 1.)

spreading to adjacent regions of a lower level. In general, the anterior end of an embryo is supposed to be the highest level. According to Child, high levels are more susceptible to injuries than lower levels, and therefore the reported experiments are bound to injure mostly the anterior end of the embryo, which is supposed to control the pattern. This interpretation (which, by the way, does not agree with the results of experimentation by the Spemann school) is, however, only a specific way of expressing in terms of metabolic level the same thing that Stockard expressed in more general terms of inhibition and velocities.

The first step to link these facts with the problems that we are studying here was taken by Newman (1908-1917) when he found that the same type of monsters could be produced by crossing widely distant forms of teleosts. Here, then, a genetic agency was found to have a parallel effect, which now brings this set of facts close to the problem of the phenocopies. Here belongs also a finding by Montalenti (1933), who reported numerous abnormalities produced by crossing species of toads all of which may be attributed to the effect of asynchrony of developmental rhythms.

The foregoing interpretations are still better supported by cases in which a single Mendelian gene produces effects very much like the ones described; there is the case of Little and Bagg (1924), of monsters in mice supposed to be inherited in a simple Mendelian way; another somewhat different one by the same authors (1929); a case of Wriedt and Mohr (1928) of such a type in cattle. Also, Little and Bagg in analyzing the abnormalities produced in X-rayed rats reach conclusions of a similar type. They find that the defects are in most cases the consequence of extravasates, produced at different times, which interfere with the normal rate of differentiation of the respective organs. In some respects, the best analyzed case, though not so simple on the genetic side and not studied embryologically, is the one found by Wright, the case of otocephaly in guinea pigs (Wright, 1934*c*; Wright and Wagner, 1934; Wright and Eaton, 1933). This heritable abnormality consists in a graded series of changes at the anterior end, beginning with a reduction of the lower jaw. (2) Then the ears are joined below the jaw by naked skin; (3) then there is only a single ear opening on the throat; (4) the mouth and upper incisors are lost; (5) the nostrils fuse; (6) the eyes become fused more or less below the proboscis; (7) and the fusion becomes complete. (8) Then the proboscis is lost; (9) the eye also; (10) also the ear opening; (11) and finally no head is left except a small median ear. Figure 16 illustrates these grades.

This type of monstrosity is inherited, though not in a simple manner, a fact that does not concern us here, however, except that we are not dealing with the effect of one mutant gene but with a combined effect of, perhaps, two. There is no comparable phenocopy in mammals, but, as we have already reported, in lower vertebrates monsters have been produced by experimental treatment of early embryonic stages which closely resemble these.

Wright's analysis of the facts led him to the following conclusions: In accordance with the experiments of Stockard, etc., which were reported above, it seems that the monstrosity is produced by an inhibitory action upon early stages of development prior to the visible formation of the organ rudiments. (This is, of course, found to be the case in all experiments on determination.) But whereas the experimental treatment produces more diffuse and general effects, the genes in question have a specialized effect of the type described as otocephaly. This means, according to Wright, that the gene effects are relatively direct and precise in their moments of action. In detail, Wright favors Child's point of view: Any agent that inhibits the metabolic processes of the early embryo before the primary simple gradient pattern has become complicated affects especially the most active region with consequences mostly upon the anterior end of the medullary plate.

Other explanations of the embryological facts are, however, possible. Lehmann (1936) concludes from his experiments that the primary cause for the formation of these monsters is probably a defect in the head organizer. This sounds, indeed, more reasonable than the idea of gradients, which has not much of a factual basis.

Reference has been made to the work of Little and Bagg in which it was shown that abnormalities in mice caused by a recessive gene and appearing phenotypically rather diversified as clubfoot, polydactyly, anophthalmia, etc., were the result of blood extravasates formed in early embryonic life. A simple embryological process then produced all those complex features. A detailed analysis of all the defects of skull, mandibles, brain, etc., combined in the picture of otocephaly showed that they all may be traced to a small number of centers of abnormality: ventral mandibular arch, olfactory placodes, cerebral vesicles, median optic rudiment, and some others. "These in turn may be related by the hypothesis that the basic factor in this class of abnormalities is inhibition of the anterior medullary plate and associated ectodermal placodes. . . ." It may be that a still earlier and more generalized stage is the critical one (see preceding paragraph). The important point remains that an early inhibition at a definite point of embryonic development is responsible for the whole chain of later events. All the types of

monsters, then, may be explained on the basis of different degrees of inhibition, acting upon different stages in development and lasting different times. The action of the mutant genes is conceived, as mentioned above, as a general inhibition, to which the regions most active at a particular moment are the most susceptible. It might be debatable whether this special interpretation is correct (a description in terms of organ-forming stuffs or organizers or determination stream could easily replace the description in terms of gradients; (see Lehmann)). But the general conclusion is certainly correct, which Wright formulates thus: "The case illustrates the extent to which morphological changes of an apparently qualitative sort may be brought about as a result of ramifying correlative effects from initial gene effects of a simple quantitative sort." We shall realize when discussing the formation of pattern that this result furnishes another example for the general correctness of Goldschmidt's views on primary pattern formation as controlled by genes.

The facts described in this chapter may be linked with the contents of the next chapter by some facts discovered recently by Bonnevie (1936*b*). She studied the development of still another hereditary abnormality in mice, pseudencephaly, caused by a recessive gene and consisting of a complete upset of the arrangement of the brain which rides like a wig on top of the head. Again, it was found that the primary cause of the defect occurs very early in development. The decisive point is that the development of the primary head mesoderm is affected. It seems that all individual developmental processes are perfectly normal but that the relative velocities of growth have been changed: the ectodermal head parts are growing while their mesenchyme surroundings are still underdeveloped, which forces the former to fold and to behave abnormally. The rest of the abnormal development is the mechanical consequence of this primary situation. In other words, the effect of the mutation is to destroy the proper timing of two major interdependent developmental processes by changing the rate of only one of them.

3. THE MUTANT GENE AND THE RATE CONCEPT

The facts reported thus far all point in one direction: they show that the mutant gene produces its effect, the difference from the wild type, by changing the rates of partial processes of develop-

ment. These might be rates of growth or differentiation, rates of production of stuffs necessary for differentiation, rates of reactions leading to definite physical or chemical situations at definite times of development, rates of those processes which are responsible for segregating the embryonic potencies at definite times. Thus far such conclusions were derived only from the facts regarding the phenocopies and similar phenomena. Originally, however, the interpretation of gene action in terms of rates of reaction was derived from a different type of facts, analyzed by Goldschmidt (1917*b*, *c*, 1920*b*), *viz.*, observed differences in rates of certain gene-controlled processes. For a special case, the pigmentation of rabbits, Wright (1916) had also derived the concept of rate of production of an enzyme to explain the action of different alleles for coat color (see page 73).

A. RATE GENES

Goldschmidt (1917*d*) first drew attention to rate genes and their importance for an understanding of gene action. He described different genetic races of the gypsy moth, *Lymantria dispar*, the caterpillars of which were different in regard to their markings. The main difference was that in some races a pattern of light markings on the back persisted throughout development; in others, it became covered during development by a dark cuticular pigment which was deposited at a certain rate with the progress of development. This rate was different in different races and intermediate in heterozygotes. Thus different genetic constitutions could be linked with different rates of production of pigment during development. Numerous curves for the process are found in Goldschmidt (1924*b*).

Simultaneously Goldschmidt studied another phenomenon which led to an explanation of gene action via rates of developmental processes. The phenomenon of zygotic intersexuality produced by crossing the sex races of *Lymantria dispar* permitted such an analysis. It was shown that a definite event in the development of intersexes, the turning point at which sex changes, could occur at different times, depending in an orderly way upon the genetic constitution of the individual. It was argued that such a perfectly orderly dependance of the time of such a change from a similarly orderly set of conditions of the sex genes could be understood only if two competing sets of reactions

of orderly but varying velocities were involved. Sex genes, then, were conceived as controlling the rate of production of sex-determining stuffs. From these two sets of facts and their genetic and embryological analysis, a generalization was derived applying the principle of rate to all genic actions. (For details see Goldschmidt, 1920*b,c*, 1927*c*.)

Many cases have since been studied which show a connection between mutant genes and rates of processes. In this chapter only certain cases will be mentioned in which the rate concept has not been inferred from the facts but where actual rates have been measured. Ford and Huxley (1927) were able to measure the rate of pigmentation of the eye of *Gammarus chevreuxi*. In the normal dominant Black-eyed form, the eye pigment first appears scarlet. It later darkens through brown and chocolate into black. In the Red-eyed mutation, the darkening of the pigment takes place much more slowly and also starts later. The end of the process, therefore, reaches a stable phase before blackening is completed. These two different rates have been plotted as curves and have been found to depend to a certain extent upon external conditions. Genetically the genes involved control either the rate or the onset of the pigmentation process.

Very nearly related to the facts concerning pigmentation in *Lymantria* caterpillars are those found by Goodrich and Hansen (1931) for pigmentation in fishes. They studied the increase in the number of pigment cells in brown and transparent goldfish in the course of development (genes *T* and *T*₁). Figure 17 shows the rate curves for the two homozygous and the heterozygous forms which resemble closely Goldschmidt's curves for pigmentation of *Lymantria*. In this category would probably also belong the results of Hashimoto (1936) with the silkworm if an embryological study had been made. There is a mutant gene in this form causing an extra pair of abdominal feet. In heterozygous condition, only the feet are produced; in homozygous condition, the next segment is also influenced and has an extra semilunar spot. In this connection, such gene actions might also be mentioned as the genes controlling later or earlier growth of feathers in the chicken according to Serebrowsky and Warren.

A whole group of cases is known in which the mutant gene affects definite growth rates. Of course, in this case, one might claim that there is no difference between the action of a gene

controlling color or shape or any other character and a gene controlling growth rate. This is true. But as it seems that all gene actions may be in the end reduced to the control of rates, such cases where actually visible rates are involved are of a special significance. Only a few typical examples may be given, which illustrate the type of processes involved. There are some cases in which the mutant gene changes the rate of differentiation without any visible changes of growth. Thus the vestigial gene

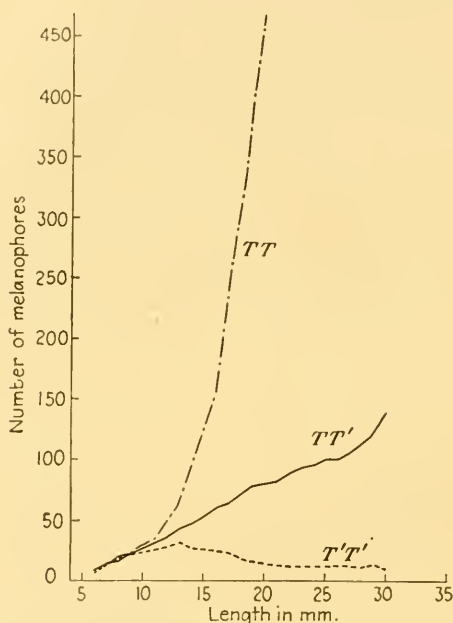


FIG. 17.—Graph of average number of melanophores in the three types of goldfish, Common TT , heterozygous TT' , and transparent $T'T'$. (After Goodrich and Hansen, 1931, *J. Exp. Zool.* **59**, Fig. 7.)

retards development during the larval period by $5\frac{1}{2}$ hr. according to Harnly (1929). More typical are the cases in which the mutant gene controls a different rate of growth processes. Studies of such cases have revealed a few facts of primary importance. Castle and Gregory (1929) showed that the differences between large and small races of rabbits, which genetically are caused by multiple genes, are, in fact, differences of rate of cell division, which begin early in development. Thus the growth

curve, though starting with eggs of the same size, becomes different from the onset of development.

Exactly the same was found by Goldschmidt (1933a) for the differences in size of geographic races of *Lymantria dispar*. Figure 18 represents curves of growth for three such races, female

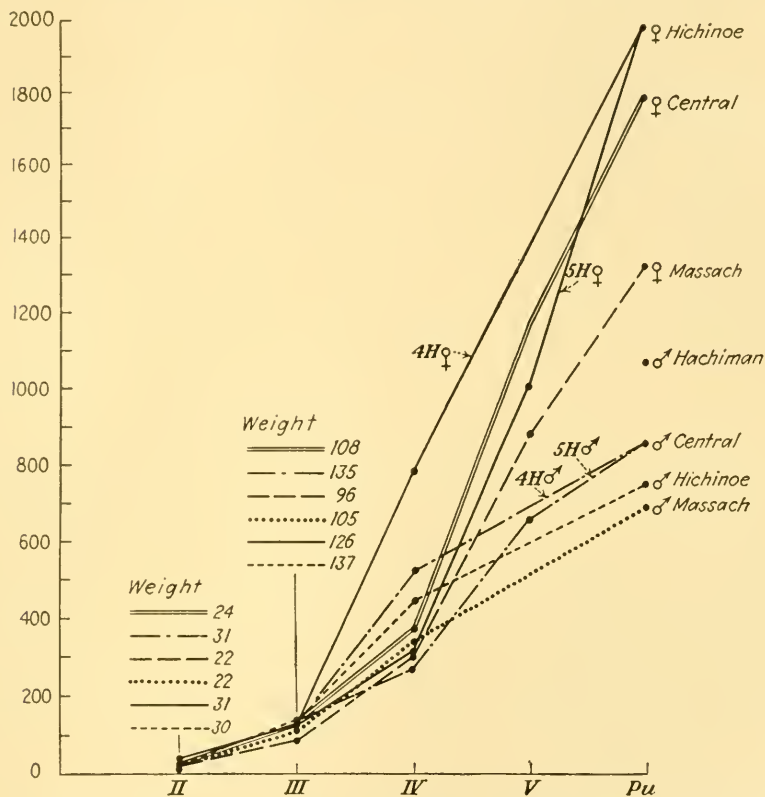


FIG. 18.—Growth curves plotting larval instars against weight in milligrams for caterpillars of *Lymantria dispar* of different size-races. (From Goldschmidt, 1933, *Arch. Entwicklmech.* **130**, Fig. 16.)

and male, with weight plotted against the larval instars. The differential growth rates become visible as soon as they are measurable.

As an example from plants, the observations of Müntzing (1932) on *Galeopsis tetrahit* may be mentioned. Here flower color and speed of development are correlated, the white-flowered plants beginning to flower later than the red ones. It was shown

that this phenomenon was due to the color genes involved, which might control simultaneously the rate of cell division. In this case, it could also be demonstrated that the respective speeds were proportional to the number of red factors present. This relation is especially impressive, since the difference occurs between white-flowering plants having or not having the red gene.

There is another characteristic feature of such cases as these: Frequently an influence of the cytoplasm upon such growth rates has been demonstrated. It came to light in both Castle's and Goldschmidt's work, and a considerable part of the work of Wettstein and his students on cytoplasmic influence in heredity (his plasmon) deals with structural differences dependent upon growth rates. (The rate of division of the protonema cells in different species of mosses is a genetic character, probably dependent upon one or two Mendelian genes.) This is, after all, not so surprising, as all rates of reaction are dependent upon the substratum in which the reaction takes place (see page 263).

B. GENERAL EXPERIMENTAL EVIDENCE

In the majority of cases that have been studied experimentally, the conclusion that the respective gene actions are of the nature of a control of rates has been deduced from certain regularities which could be described in the simplest form in terms of rates. It might be said that almost all careful investigations in this field have corroborated the general concept that genes act by controlling rates of processes or reactions responsible for orderly development. The general mode of attack has been quite different in different cases, which in part have already been mentioned in the foregoing chapters.

1. A Typical Case.—We begin with the case of the vestigial alleles and phenocopies, which was reported without interpretation, because in this case, genetics, development, and phenocopy effect are known. The genetics of the case—leaving aside for later consideration the interesting dominance conditions—give evidence of a remarkable quantitative order of visible effects within a series of multiple alleles, their heterozygotes, and compounds. Mohr (1932) has made a thorough investigation of the allelomorphic series Wild type—nicked—notched—vestigial—No-wing. Figure 19 shows the average phenotype of the different homozygotes, heterozygotes, and compounds as they

appeared in Mohr's work. Above the pictures the constitution is marked, and below the pictures the percentage of individuals showing the phenotype (percentage of penetrance). We realize that the normal wing of the wild type ($+^{vg}/+^{vg}$) occurs also in the heterozygotes between wild and notched (vg^{no}), wild and nicked (vg^{ni}), and wild and vestigial (vg) and in the homozygous nicked fly. The compound nicked-notched shows that 0.2 per cent flies with a nick and 100 per cent scalloped flies are obtained only in the compound vestigial-notched; all further data may be read from the figure.

Here, then, a series of alleles (into which, also, the heterozygotes and compounds fit) produce a perfectly orderly series of effects, with a simple quantitative arrangement of the phenotypes resulting. It begins with no visible effect and leads through the steps of a small effect in few, in many, in all individuals to increased and still more increased effect up to the maximum that is physiologically possible, and this maximum is at the threshold of lethality.

The study by Goldschmidt (1935c) of the development of these quantitatively different grades of scalloping of the wings showed, as reported above, that development is normal up to a certain moment, when a degeneration of the tissue of the wing margin sets in and proceeds up to a time in development when no further destruction of wing area seems to be possible, and from then on the rest of the wing finishes its normal development. It was further shown that, so far as the evidence goes, the earlier and earlier onset of the degenerative process produces a greater and greater amount of wing destruction. Thus the different genetic constitutions are linked with a process that contains a definite time element. Taking into account further the phenocopic effect (see page 9) of the same type produced if the temperature shock or X-ray shock is applied at the proper time, (as well as the facts to be reported later on a parallel shift of the phenotype by dominance modifying genes), we may form a picture of the whole process in terms of rates. At the present juncture in the analysis of the case, this picture might be differently conceived in its details; but in its general form it must be of the following type: The process of degeneration of the wing tissue which results in scalloping may be due to the presence of something that prevents—physically (permeability, viscosity) or

chemically (poison)—further differentiation or, by lysis, destroys existing tissue. Or it may be the consequence of the lack of something necessary for differentiation, an insufficiency, *e.g.*, of a growth substance, a vitamin. If we use first the latter concept for the sake of simplicity, we could represent the case in the form of the diagram (Fig. 20). The series of *vg*-genes controls the production of the growth substance in question which has to be present at each stage of development in sufficient quantity to

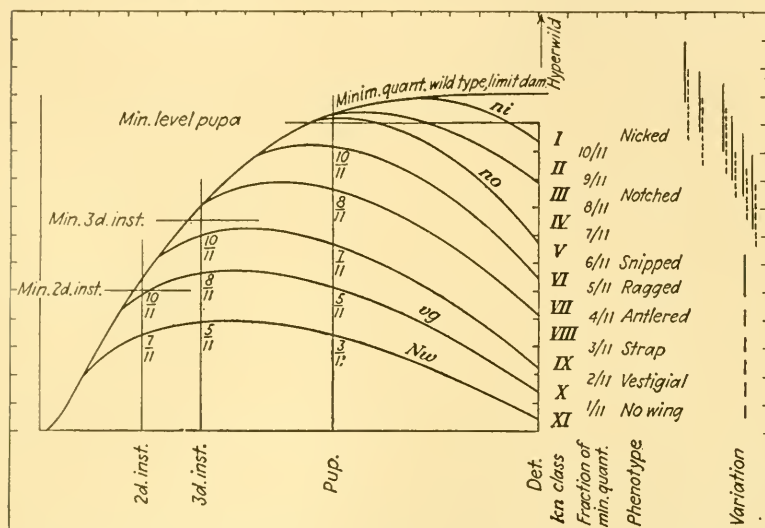


FIG. 20.—Graphic representation of the action of the different *vg*-alleles upon destruction of wing area. Abscissa instars; ordinate wing growth. (From Goldschmidt, 1937, *Univ. of Calif. Publ. Zool.* 41.)

insure normal differentiation. In the Wild type and in all compounds producing the Wild type, the rate of production of this substance has to be above this minimum. As the production must keep pace with the normal growth of the wing *Anlage*, the top curve in the diagram might represent as well the growth curve of the *Anlage* as the curve of production of the growth substance. As the facts of development show, the deficiency of this substance begins earlier and earlier in the progressive series of alleles and continues to increase almost up to the end of wing development, as shown by the continuous degeneration. The curves for the production of this substance must therefore begin to drop at a certain point in development and continue to do so

to the end. If the size of the *Anlage* at each moment of normal development is given by the normal growth curve on top, the ordinates of the other curves ought to indicate also the size of the degenerating *Anlage* at different times, in fractions of the normal size at the same time. The curves for the different alleles have really been drawn according to the values of these fractions, actually found and noted in the diagram. The resulting phenotype is marked on the right side. The diagram, then, represents all the facts mentioned in terms of rates of production of something and apparently this general form, which might be varied considerably in details, is the only consistent method of representing all the facts. (According to Kirchhoff's classic definition, an explanation is the shortest description of all the facts.) As mentioned before, the same facts may just as well be presented in terms of production of something that destroys wing tissue. If we accept this reciprocal type of representation, the curve (Fig. 20) means, besides the growth curve, the curve of production of the substance in question which from a certain moment on destroys tissue. This representation seems at first sight less probable. But a most remarkable parallel is available, which makes it worth while to investigate whether there is not something more than a superficial resemblance behind the two phenomena. In a series of papers on the kinetics of bacteriophage, Krueger (see 1936) found the following facts:

If a mixture of phage and growing bacteria is kept, the increase of phage depends upon the bacterial growth in so far as it does not occur without the latter. But the rate of increase of phage is considerably greater than the rate of bacterial reproduction, and therefore the ratio of phage to bacteria is constantly increasing. When a certain ratio in favor of phage is reached—the lytic threshold—lytic destruction of bacteria begins and proceeds rapidly to completion. The time of onset of this destruction is proportional to the initial concentration of phage in the mixture. Phage may be inactivated and reactivated by differentiations. In addition, in the presence of manganese, the lytic action begins earlier; this is solely an effect upon the threshold, *i.e.*, the quantity of phage/bacterium requisite for lysis. Figure 21 represents Krueger's graph for these experiments, which shows a perfect model of the vestigial case. The growth curve of bacteria corresponds to the normal wing growth in *Drosophila*. The same

curve might also represent the increase in phage if it would be proportional to the bacterial growth, as has been silently assumed in the vestigial case for the production of the decisive stuff. This assumption, which works in case of a growth substance, would not work in the case of production of a lytic substance, as we must account for the different time of onset of

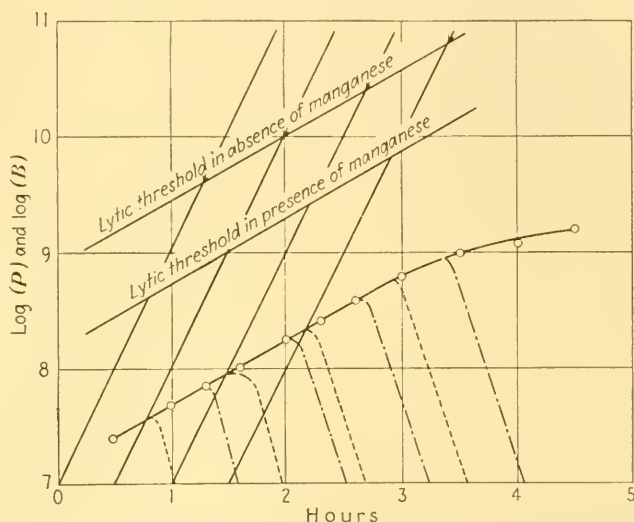


FIG. 21.—Graphic representation of bacterial growth, phage production and lytic ratios with and without MnCl_2 . Originating in the bacterial growth curve o are the curves of bacterial lysis with MnCl_2 (.....) and without (—). Above are two lines paralleling the logarithmic phase of the growth curve. Both are crossed by a series of steep curves representing phage formation for various initial phage concentrations. The intercepts of these latter lines with the two parallel lines indicate attainment of the lytic phage bacteria ratios requisite for lysis. At corresponding time intervals on the curve for bacterial growth the curves of lytic destruction of bacteria begin. (From Kroeger and West, 1935, *J. Gen. Phys.* 19.)

action. In Krueger's diagram, the different times of onset of lytic action and the consequent dropping of the curves for bacterial growth are visible, and their similarity to the curves for wing growth is obvious. Here we find, in addition, the steep curves for growth of the phage drawn for four different initial concentrations. Their intercept with a line parallel to the growth curve, representing the assumed ratio of quantity phage/bacterium necessary for lytic action, is then the lytic threshold. In the vestigial curve, this threshold has been indicated directly, but it might as well be represented as in Krueger's graph. The

upper parallel indicates the lytic threshold in the presence of Mn. A parallel to this would be the action of the dominigenes (or temperatures) upon the *vg*-curves.

It is clear that we could use the graph for the phage also to describe the vestigial case, *viz.*, under the former assumption that the genes produce here a lytic substance which acts upon the wing as soon as a threshold value is reached. The main curve of Krueger's graph would then represent the growth and subsequent lysis of the wing; his curves for phage production would be the curves for production of the lytic substance; the initial concentration of phage would be the different alleles of *vg*, and the manganese curves would represent the action of modifiers which will be studied later. The phage model then contains exactly the system that we postulated for gene action and especially the vestigial case: a growth curve; an onset of destruction at definite times; a proportion between this time and the basic concentration (see later the theory of multiple alleles); and threshold values, which might be modified by other substances produced by modifying genes. The parallelism, if not more significant, shows at least one thing: The type of genic actions as derived from the author's work is actually found in comparable processes in nature.

It ought to be added that Mohr in his study of this allelomorphous series drew some similar conclusions, in so far as it was possible without knowledge of the development. He speaks of the different potencies of the alleles in producing the respective amounts of scalloping and assigns definite numerical values to these potencies, a method of description that was introduced by Goldschmidt (1912) in his work on the potencies of sex genes. He gives the highest value to the potency for production of the Normal wing (30 for one gene) and the lowest (6 to one No-wing gene) as estimated, of course, from the phenotypical result. These values are found at the base of Fig. 19. The threshold for the first indication of a Nick, then, is found at potency 37. He discusses further the probability that these potencies act by controlling reaction velocities.

It is probable that similar cases may be found in plants, as might be inferred from Van Overbeek's (1935) work. He studied the recessive character *nana* in corn which causes an inhibition of growth of the mesocotyl. He studied the behavior of the growth hormone (auxin) in this mutation and found that

nana gives off less auxin from the tip of the coleptile and also that it grows less with the same amount of auxin. It was found that the reason for both is that in *nana* auxin is destroyed at a higher rate. The reason for this seems to be a change in oxidation reduction. In this case, the result is only dwarfism, but a similar effect might in other cases lead to tissue destruction, as in the vestigial wing.

There is one case existing in plants that falls in line with the facts discussed in this and the foregoing chapter and has been used also to derive a corresponding explanation. Oehlkers (1930-1935) analyzed the *Cruciata* character of *Oenothera*. This hereditary pathological trait might be compared to cases of Homoeosis in *Drosophila*, as homologous organs replace each other. *Cruciata* flowers are sepaloid, the petals being more or less transformed into sepals. All transitions exist from petals with a trace of sepaloidity through different mixtures of petal and sepal tissue to pure sepals. The trait (which had already been studied by de Vries and others) behaves as a simple Mendelian recessive. The grade of sepaloidity is also inherited, is typical for each *Oenothera* complex, and remains constant in crosses. The phenotypic effect of different combinations follows simple quantitative rules and is such as expected, if each of these *Cruciata* genes—assuming them to be members of an allelomorph series—has a definite quantitative effect in regard to the *Cruciata* character. The case therefore resembles most closely the case of the sex genes in *Lymantria*, where also a series of different conditions of the gene exist, which in all combinations have the proper additive effect which can be calculated from the individual effects. Oehlkers represents his facts, then, using the type of the diagram introduced for *Lymantria* and in terms of assumed quantities of action of the respective genes. His diagrammatic representation of the facts takes as a basis a quantity of 10 for one definite complex with complete sepaloidity and of 42 for one with complete normality. Parallel to the case of intersexuality in *Lymantria*, it is assumed that everything above 26 is normal, below 16 sepaloid, and between 16 and 26 intermediate in five classes (Fig. 22). The different combinations of complexes with *Cruciata* must then give consistent results if definite quantities are assigned to the individual actions. This is the case.

It has to be added, however, that in this case the presence of a series of multiple alleles is made probable but not strictly proved, as the special conditions of complex heterozygosis in *Oenotheras*

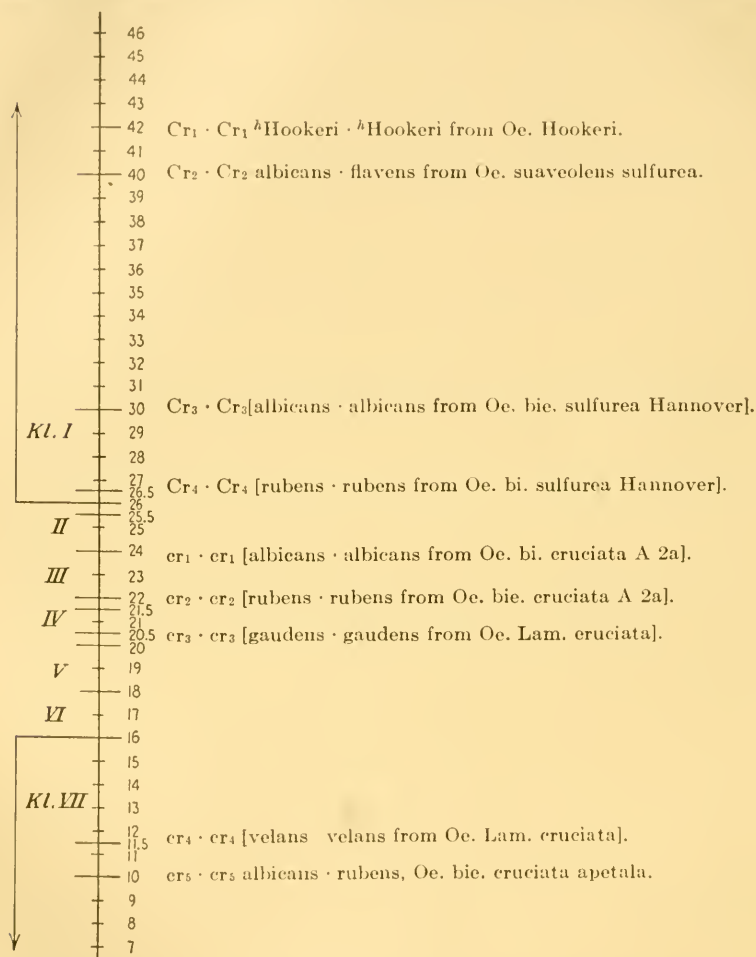


FIG. 22.—Graphic representation of the relative effects of the genes *Cr* - *cr*. In brackets, combinations that may not be obtained. KI I-VII, phenotypic classes; *cr* 1-5, cruciate genes of increasing potency. [From *Oehlkers*, 1930, *Ztschr. f. Bot. (Oltmann Festschr.)*.]

make a complete proof rather difficult. It would be interesting to try to formulate a more detailed view of genic action in this case. Unfortunately, the basic facts concerning developmental

mechanics of the case are unknown. A zoologist would suspect that the normal differentiation of sepals and petals has to do with a process that we shall later discuss as stratification of determining substances (which occurs a long time before visible differentiation). Sepalody would then be the effect of insufficient segregation of such stuffs in the flower bud. If this were the case, an interpretation parallel to the *vg*-case involving velocities of definite processes might be developed easily. Unfortunately, the physiological facts are lacking. But there is one significant fact strongly pointing in the direction of such a general explanation: Oehlkers (1935) found that the *Cruciata* gene increases the rate of differentiation of the plant and made it even probable that this increase is proportional to the relative strength of these allelomorphs.

2. The Threshold Concept.—Before reporting further cases of the same type, we must consider the threshold concept, which we are facing here for the first time and which will reappear on many occasions. The diagram (Fig. 20) shows in the curve for the Wild-type wing (on top) that the production of the decisive substance always has to be above the necessary minimum, the threshold, to insure normal development (or, in the reciprocal conception, below the threshold). We could imagine that many more such curves above the normal curve exist, all of which would be above the threshold and therefore control different degrees of Wild-type, *viz.*, plus minus hyperwild. We shall return to this special point in the chapter on dominance and shall discuss here only the general features of the threshold concept. Early in the development of the theory of genic action by rates of reaction, it became clear that the explanation of many details requires the assumption that the products of those reactions which might generally be called determining stuffs act only when they have reached a minimum concentration, *i.e.*, a threshold level. To this may be added the conception that there is also a maximum of response: Above a certain level of concentration, no increase in response is possible; *e.g.*, an increase in the wing-growth substances will not change the effect, the maximum of which is the Wild-type wing. This level of possible maximum response may coincide with the minimum threshold, as in the case just mentioned, or it might also be higher. We shall meet later with examples.

The threshold conception had already been used by Goldschmidt in his first analysis of the phenocopic effect (1920*b*), as well as before, in his first analysis of intersexuality (the epistatic minimum, Goldschmidt, 1912, 1920*c*). Wright also (1916) had realized its importance in explaining the action of the pigmentation genes in guinea pigs (see page 88), which he conceived in a way similar to that presented in Goldschmidt's simultaneous work. It has since been used considerably by many authors who discuss questions of rate (Crew, Haldane, Huxley, Plunkett, Wright, Mohr, *et al.*; see also its interesting application to certain problems of sex determination by Dobzhansky and Goldschmidt, 1934*c*). We shall meet it over again in connection with different problems. Here only one of its aspects will be mentioned, which, though highly important, has not yet been analyzed sufficiently. In Mohr's table (page 57), we found that the lowest members of the *vg*-series, which produce only a small nick in the wing, do it not in all individuals but only in a small percentage. In higher gene combinations, this percentage increases finally up to 100 per cent, parallel with a quantitative increase of scalloping. Here is a very important problem from the standpoint of gene action.

Timofeeff-Ressowsky (1926) has called this peculiarity of the action of some genes or alleles, which in *Drosophila melanogaster* is typical for some lower alleles in a series and which is in other species of *Drosophila* the most frequent form of gene expression, the *penetrance*; this term might sometimes be useful for a short description of such cases. An explanation of the phenomenon in terms of threshold is suggested, when this phenomenon appears as a member of a simple quantitative series of effects at one end of the series, as in the *vg*-case. Here a further feature is also added, *viz.*, a parallel increase of the percentage phenotypic effect (*penetrance*) with the increase of the degree of the phenomenon, in this instance the amount of scalloping. (Timofeeff calls this the *expressivity*, a term that might lead to rather dangerous misunderstandings.) Such a series of facts of an orderly linear nature requires an explanation of the same type. This is easily conceived if the threshold concept is applied. To show that the same general type of interpretation may work with different conceptions in detail, we may apply two such conceptions to the vestigial case as follows:

1. The time at which an event leading to degeneration is still possible is limited, as we saw, to a definite stage in wing differentiation. This time would then constitute a limiting value. The action of the gene in question may require so much time to reach the necessary concentration for action, or, in the reciprocal conception, the curve of production of the growth substance may drop below the threshold at so late a time in development, that in either case the event approaches the limiting time. The normal variation in the time of developmental processes may then cause a larger or smaller part of the curve of variation of developmental time to cover the time at which the gene-controlled process takes place. The result is that all individuals belonging to the part of the curve beyond the limiting value for possible changes remain normal.

2. The same result would be obtained if the time of differentiation remained constant and the moment at which the curve drops were variable, or if the threshold concentration for the stuff in question were variable or another member of the system or some or all would vary.

In general terms, then, the phenomenon would result from the general fact of fluctuation of the particular processes of development in conjunction with the existence of thresholds for the integrating processes.

An actual example of this type in which some of the elements are known is the following: In *Lymantria dispar*, male intersexes of different grades may be produced by combining in appropriate crosses sex genes of typical but different valencies. If, for example, a constant female determiner of high valency, a so-called *strong F* (which has turned out to be a cytoplasmic quality), is combined with one constant male determiner of low valency or a weak *M* (which is inherited within the X-chromosome), the second *M* in the male formula ($2X = \sigma$) may be taken from races of different valencies. In the balanced system of sex determiners, which might be written F/MM , which is the general formula for males, the valencies have been combined as $F_{str}/M_w M_{var}$, M_{var} meaning that this *M* alone will be varied in different combinations built up by crossing. The respective valencies of *M* in different races are known from other experiments. Introducing then *M*-genes of the highest valency (= strong) through intermediate stages to the lowest valency (= weak) into individuals of this

formula, the sexual balance is shifted correspondingly in favor of F . The result is that an ascending series of male intersexes is produced, beginning with a combination giving normal males and leading through all stages of low to high intersexuality, finally to sex reversal, *i.e.*, females. The actual result of such a series of replacement experiments is represented in the following table.

TABLE 5.

Strong F from race	Very weak M from race	Second M of increasing strength from race	σ	Intersexual σ grade (black line = range of variation)						φ (genetic σ)
				I	II	III	IV	V	VI	
Tokyo	Hokkaido	Hokkaido								————
Tokyo	Hokkaido	Berlin								————
Tokyo	Hokkaido	Russia					————	————		
Tokyo	Hokkaido	Korea			————	————	————	————		
Tokyo	Hokkaido	Kumamoto	————	————	————					
Tokyo	Hokkaido	Kyoto	————	————						
Tokyo	Hokkaido	Tokyo	——							

Here we notice the phenomenon that is of interest in the present discussion. If the sexual balance is shifted so that the lowest grade of intersexuality is produced, it does not happen to all individuals but only to a certain percentage, which increases with increasing grade of intersexuality. There is obviously a threshold, or limiting value, for F/MM at which intersexuality begins (called the *epistatic minimum* in this case). And there is obviously a fluctuation of the value F/MM around a mean—whether as a modification or produced by modifying genes is irrelevant—with the consequence that only individuals belonging to the part of the range of variation beyond the threshold become intersexual. (Pictures of such a series of male intersexes are given in Fig. 35, page 194.) The same will be found at the other end of the series, where a high degree of intersexuality fluctuates into femaleness. It might be added that recent discussions of the special problems of sex and intersexuality by Dobzhansky and Goldschmidt (see page 66) have added the possibility that the cytoplasmic factor which is designated as F , because working in the direction of female determination, might in fact be some-

thing that determines the position of the threshold for the successful action of the *M*-genes within the X-chromosomes. It may be added, also, that the other example mentioned in the last chapter, Oehlker's *Oenotheras*, show the same threshold phenomenon (see Fig. 22). At the threshold limits (26 for normal versus low-grade sepaloid), a fluctuation of some individuals across the border line occurs. Furthermore, a number of genotypes are found of different quantitative value, phenotypically alike because located beyond the threshold, and strictly comparable to the hypermales and females in *Lymantria* and the hyperwild in vestigial flies.

3. Penetrance.—The facts reported on pages 65 to 68 brought us again into contact with a problem that had been occasionally mentioned before, the discussion of which finds its proper place here. Timofeeff (1926) introduced the term penetrance to describe the fact that the phenotypic effect of a gene does not always take place in 100 per cent of the individuals homozygous for the gene. In the vestigial case (see Fig. 14), the genes *vgⁿⁱ/vgⁿⁱ* had zero penetrance; and the nicked-notched compound, 0.2 per cent penetrance. This term might be used for descriptive purposes, provided one realizes that penetrance is a phenotypic result, which may have many underlying reasons such as the absence of genetic modifiers necessary for the production of the effect, the existence of a threshold for visible effect which is controlled genetically or by outside conditions, or a weak potency of the gene in question, combined with a threshold that is not reached. Of these possibilities the first one may be omitted here, for if Mendelian segregation of modifiers, present in the line, leads to definite percentages of visible effects, it amounts to a question of Mendelian segregation with genes of otherwise invisible effect. If such modifying genes, however, control threshold conditions, the problem is the same as all threshold problems in regard to the details of explanation. But the numerical values of penetrance are again the result of a Mendelian segregation, this time of modifiers for the threshold of visible action of the main gene.

In the preceding section, we mentioned the cases in which obviously a low percentage of penetrance was the result of the presence of a threshold in such a position that the always present fluctuation of the decisive process allowed only a small number

of the individuals to reach the threshold. In those cases, the position of the threshold was determined by the quantity of a determining substance or the time of its onset. It may be safely assumed that in most cases of penetrance this is the actual situation. But it must be kept in mind that in each case the action of modifying genes will first have to be excluded, before any conclusion upon gene action may be drawn from the material. We may conveniently group the material into the following types: (1) genes that under normal conditions do not manifest their action but have a visible effect under other definite conditions; (2) genes that under standard conditions (and excluding modifiers) produce a visible effect in a certain percentage of the individuals containing the gene. It is understood that in such cases the normal individuals must be proved to have the same genetic constitution as the others. In this case, genetic or environmental conditions may be shown to control the percentage of changed phenotypes. Examples for these types of behavior are abundant in genetic literature. We shall report only those in which experimentation has yielded information relevant to the problems under discussion.

There is the frequently quoted case of reduplication of legs in *Drosophila* due to a sex-linked mutant gene. Hoge (1915) found that this type appears only in a certain percentage of the homozygous flies but that if reared at a low temperature the percentage increases from between 10 and 15 to between 30 and 68 per cent. The action of low temperature was found to be limited to a sensitive period which is situated very early in development. This is, of course, to be expected, as the action must take place before the imaginal disks of the legs are finally determined. One might conclude from the facts that the action of the mutant gene takes place at a time very near to the time of final determination of the *Anlage*, a time limit beyond which a fluctuation occurs depending upon temperature (see end of this section, page 72). Similar results have been reported by Morgan (1915*b*) for the character abnormal abdomen where humidity is the decisive agent, by Komai (1926) for crippled legs in *Drosophila*, by Astauroff (1930) for the mutant tetraptera. (Here the penetrance increases from 1 to 35 per cent with a rise in temperature from 17 to 27°C.)

Of a somewhat different type is the work of Wright (1934*a*) on extra toes in guinea pigs. This character is not the result of a

single mutation but seems to be caused by a major differential factor and some additional minor factors. By selection and inbreeding, different lines were isolated, characterized by different percentages of penetrance of the character. In this case, it was also proved that the normal individuals had the same genetic constitution as the four-toed ones. Some of the facts pointed in the direction of external influences upon the percentage incidence of the type, but mammals are unsatisfactory material for such experimentation. Wright realized also, just as Goldschmidt had in the cases reported before, that the problem comes down to the question of a physiological threshold, which is reached or not reached under certain combinations of genetic as well as environmental conditions.

A systematic inquiry into this problem has been made by Timofeeff (1925, 1929a, b, 1934) who worked with *Drosophila funebris*, a species in which most of the mutants do not show a 100 per cent effect but a lower percentage of penetrance under standard conditions. The mutant in question is *venae transversae incompletae (vti)* of *D. funebris*, exhibiting an interruption or absence of the cross veins of the wing. Vti is an autosomal recessive which requires in addition the presence of another gene for visible manifestation. Furthermore, there are present other modifying genes which influence the percentage of individuals exhibiting the defect, *i.e.*, the penetrance. By means of selection, lines could be isolated which showed from 41 to 100 per cent penetrance, respectively. (There could also be isolated lines differing in the quantitative amount of the defect and in its specific pattern and symmetry. These facts do not pertain to the problems of this chapter.) With these selected lines, experiments were performed which proved an influence of temperature action upon the percentage manifestation, but only in some of the lines. In general, the percentage of manifestation decreases with increase in temperature. Thus 13°C. gives 97 per cent, and 28° gives 74 per cent if the temperature is applied during a sensitive period in the first half of larval life. But there is another sensitive period in pupal life where temperature acts reciprocally; a rise in temperature produces a small increase in penetrance. The explanation that Timofeeff gives for these facts falls in line with all the general conclusions that we have presented in former chapters. During the early sensitive period, the processes that

are necessary for the cross-vein formation, *e.g.*, the formation of morphogenetic substances, are speeded up by temperature action. In the second sensitive period, coinciding with the actual formation of the veins, the amount of these substances is determined, but the time of development may be differentially changed by temperature action. This is, of course, the same type of interpretation that has always been found for gene-controlled processes, following Goldschmidt's theory of *timed velocities*.

But the decisive point has not been touched here: why is the effect produced in different percentages of individuals? This part of the problem requires, no doubt, some form of the threshold concept combined with the conception of a certain fluctuation of the effect, as derived above for the cases studied by Goldschmidt. If this fluctuation takes place near the level of the threshold, a more or less considerable part of the range of fluctuation may fall above the threshold. We have already emphasized this point in the last section. This shift of the curve of fluctuation of some decisive process beyond the threshold may, however, be brought about by an action of temperature or of so-called modifying genes, *e.g.*, as a shift of the mean of fluctuation toward or away from the threshold value; or as an increase or decrease of the range of fluctuation of this reaction product; or as a shift of the threshold value for the action of that substance. Then penetrance, as far as it is not hidden segregation, is a phenomenon of threshold combined with statistic variability of the products of gene action. In a recent paper on the scute gene, Child (1936) applies the same concept to the process of bristle formation and illustrates it by the same type of diagram that Goldschmidt used in other cases.

4. Further Evidence.—We begin with work that was undertaken to find out whether an insight into the action of the mutant gene could be obtained by the use of quantitative methods. Some of this work has been reported in earlier chapters (see pages 31–34), or parts of it have been mentioned in other connections.

The first author who had derived the rate concept from experiments on somatic characters produced by a series of multiple allelomorphs was Wright (1916). Almost simultaneously Goldschmidt derived a rate concept from his work on the multiple allelomorphs of sex genes (1917*b*) and pigmentation (1917*d*),

which led to a generalization of the idea. Wright found a series of allelomorphs of the albino type in guinea pigs, which produced an orderly effect upon skin color and which could be seriated. The general nature of the effects suggested that the albino series has to do simply with the rate of a process that is essential to all melanin production. But a difficulty was met when the effects of the series of genes were studied in relation to the underlying constitution of black fur, because it was found that the order of effects was not the same. But this might have been due to secondary processes in the physiology of pigment production, *e.g.*, threshold conditions. We shall return to this special point in a later chapter (see page 88), where the details of the case will be reported. Here it suffices to say that a later, more complete analysis (Wright, 1925) led the author to confirm his earlier views that the factors of the albino series determine the rate of some one process fundamental to all pigmentation.

In *Drosophila*, Plunkett (1926) first applied the concept of gene-controlled rates to the results of his experiments. The school of Zeleny (see page 75) had already shown that a gene-controlled character, the number of facets in the Bar eye, varies reciprocally as the temperature at which the flies were raised. They expressed the results in terms of the temperature coefficient for the rate of facet formation but did not conclude that the mutant gene itself acts by changing the rate of some process, as Wright and Goldschmidt had done. Plunkett used for this experiment the gene *Dichaete* which removes certain bristles on the thorax of *Drosophila*, especially the dorsocentrals. This effect, as usual, is influenced by modifiers and external conditions, and it reacts most regularly to temperature changes and, according to Plunkett, without a sensitive period. Table 6 gives the data for mean numbers of the posterior dorsocentral bristles on one side of the body (1 in the Wild type).

Plunkett analyzed these data mathematically. As only a single bristle is involved which is produced at a definite time, the concentration of a bristle-forming or a bristle-suppressing substance must be involved.¹ The effect may then be produced either by an increase, relative to other developmental processes, in the rate of a reaction, breaking down a bristle-forming sub-

¹ It is not known whether these mutants prevent bristle formation or destroy already formed bristles, as is the case in vestigial wings.

TABLE 6
(From Plunkett)

Degrees Centigrade	<i>M</i>
14	0.690
15	0.600
17	0.581
20	0.439
21	0.364
24.5	0.266
25	0.252
27	0.124
30	0.054

stance or forming a bristle-suppressing substance; or by a decrease relative to the other developmental processes in the rate of such reactions. (Note the parallel to the vestigial case). It is known, of course, that the general rate of development increases with increase of temperature, and therefore the bristle-forming reaction must have a specific temperature coefficient (as had been assumed by Krafka, 1920*a*; Goldschmidt, 1920*b*; and others in their cases). The fact of increase of bristle-destroying effect with temperature points to the second alternative—decrease of rate relative to general development. It is then assumed that the concentration of the bristle substance is proportional to the mean number of bristles produced and that the rate of the decisive reaction that reduces the bristles also is always proportional to that concentration. The total time of this reaction is calculated to be proportional to the total time of development at all temperatures within the vital optimum. Now, the difference between Wild type and *Dichaete* is that in the latter a reaction takes place that may be described as bristle destroying. This reaction of the *Dichaete* gene, then, is to produce a catalyst which catalyzes the bristle-destroying (or obstructing) substance with a definite velocity proportional to its concentration. (Note, again, the parallel to the vestigial case and the phage.) From these premises, Plunkett proceeds to calculate the thermal increment for the bristle-reducing reaction on the basis of an irreversible monomolecular reaction, using the data for temperature-bristle effect and those for time of development. Furthermore, he calculates the effect of different temperatures as expected if the equation that was used actually applies. The calculated expectations fit very closely the data of the foregoing table. The

details of these calculations, *e.g.*, value of μ , point to the assumption that the reaction in question, produced by the *Dichaete* gene, is the decomposition of a thermolabile catalyst. And whereas the effect is bristle or no bristle, there must also be involved a threshold value for bristle-removing power. The *Dichaete* gene, then, is assumed to be a catalyst which catalyzes a chain of reactions which accelerates the (in itself spontaneous but otherwise infinitesimally slow) decomposition of a thermolabile bristle-forming catalyst by catalyzing the production of a destructive catalyst. It must finally be assumed that all genes act essentially in this way. Although he comes to just the same conclusions as the aforementioned authors, in this analysis Plunkett has delved further into the details of chemical kinetics than any other investigator and has shown that the rate concept of genic action also stands the test of subtle mathematical treatment. It might be added that the kinetic side of this work agrees again most remarkably with the work on the bacteriophage, but the actual embryological processes are not known as in the vestigial case.

Considerable work has been done with the eye mutants of *Drosophila*, which lend themselves to quantitative treatment because the number of ommatidia is a suitable numerical character. We have discussed Zeleny's and Krafka's work, which has been carried further by Driver and Hersh, whose experiments on temperature action and the sensitive period were reported. In these experiments, the following additional results were found (Driver, 1931). The temperature effect, *viz.*, the increase in facet number per degree of decrease of temperature, follows a geometrical formula which Driver expresses as $(1 + r^n) = F_1/F_2$, where r equals the rate of change, n the number of degrees decrease in temperature, F_1 the facet count at the lower, F_2 that at the higher temperature. This progressive effect shows a definite change in rate at 21° in *Bar* flies but not in *Ultrabar*. This action of temperature occurs during the sensitive period; but the length of this period (as percentage of larval life) in this case is not the same at all temperatures, becoming smaller with increase in temperature. *Ultrabar*, however, does not show this variation but shows a change with the temperature, of the onset of the period relative to developmental stage. In addition, it must be stated that the normal eye shows very little of all

these temperature effects. An analysis of these facts was made by trying to fit them to the different formulas for temperature action upon chemical processes. They did not fit either of them, and Driver therefore concludes that the series of Bar genes affect different simultaneous reactions differentially—either retarding the rate of facet formation or changing the limits of the effective periods or both more or less—and that these changes, in addition, do not parallel the simultaneous changes of rates of general developmental processes (differences in temperature coefficient). Within the sensitive period, the rate of facet formation seems to progress evenly. Altogether, then, the facts point to an action of the mutant gene upon the rates of closely interwoven but simultaneous reactions, as postulated in Goldschmidt's theory of development. A better knowledge of the development of the Bar eye might help to a better understanding of the processes involved. Chen's (1929) findings that the very young Anlage of the Bar eye is not smaller than a Wild-type eye points to a process parallel to the one reported for vestigial. We shall meet the same set of facts many times in later chapters, where additional facts will be reported.

But one more recent investigation is to be mentioned because it will possibly reduce the Bar case to the same type of processes that we described for vestigial. In a paper dealing with the action of the *vg*-gene upon the expression of the Bar series, Margolis (1935*a*) finds evidence that actually the effect of the *B*-gene may have nothing to do with the process of formation of ommatidia but is concerned rather with the production of something that destroys the material for ommatidia (see also Wolsky, page 32), which would bring the Bar case into line with the vestigial case. He found that the presence of *vg*, which, as we know, retards development, decreases the number of facets. This would be the case if a facet-destroying action of Bar were prolonged by lengthening the time of its action. All the data presented above would be interpreted in terms of a system of reactions in time, which Margolis develops tentatively along lines similar to those developed by Goldschmidt in his analytical work.

In a quite recent paper (Margolis and Robertson, 1937), Margolis modifies his interpretation somewhat. Certain irregularities in the behavior of the sensitive period in Wild flies are

interpreted as due to a collaboration of facet-forming and facet-destroying processes. The catalytic action of the Bar gene might then mean an acceleration of the destroying processes. This interpretation, of course, does not change the principle involved.

It is not possible to record here all cases in which the application of the rate concept to gene-controlled processes has led to a better understanding. We shall have to discuss some further examples in connection with other problems. Only a few more cases may be mentioned as types of applicability of the concept to various processes different in detail.

A typical gene-controlled character with a visible action in time is the molting of insects between the different instars. It is known for the silkworm (Tanaka, 1916; Ogura, 1932) and for the gypsy moth (Goldschmidt, 1924*b*, 1933*a*) that races exist with different numbers of molts (3 to 5 in the silk worm; 4 to 5 in *Lymantria*). The genetic difference involves a series of multiple allelomorphs controlling the different types. Their effect may be shifted by the presence of modifying genes (Ogura) and also by external conditions like feeding with coal dust (Nagai)¹ or hunger (Nagamori; Goldschmidt).² From Goldschmidt's work on the growth curves of such races, it is clear that the number of molts is determined independently of growth in general. The last molt, pupation, of course sets an end to further molts, and this is determined by a definite concentration of a hormone produced in the *corpora allata* near the brain (Wigglesworth). Ogura, who made a detailed genetical analysis of the case in the silkworm, came to the conclusion that all his facts could be harmonized by the assumption that the different allelomorphs control the rate of production of this hormone, which acts when a threshold value is reached. Modifiers and external conditions will then act in the same way as described above for other cases.

Of a very different type is the following example which shows how the rate concept accounts for complicated morphological changes. In analyzing the corkscrew type of deer horns, Rhumbler (1929) found that the normal growth requires the exact timing of two processes, *viz.*, the rate of growth of soft preosseal connective tissue and the rate of the ossification ascending from below. If the latter process has too low a rate, the

¹ Quoted from Ogura.

² Unpublished.

corkscrew horn will result by the action of gravity upon the not sufficiently supported tissue.

Only one more example might be added from a different field of knowledge to show how many problems might be approached and coordinated with the rate concept. I mention the work of Kühne on the hereditary abnormalities of the human vertebral column and its interpretation by Eugen Fischer (1933). It was shown that such abnormalities are inherited in a simple Mendelian way. It is not the individual variation that is inherited but a general tendency to shift the limits of the subregions of the column anteriorly or posteriorly. In identical twins, the type of shift is identical. A phylogenetic shift, comparable to these, may also be observed when comparing different types of apes and monkeys. Fischer has tried to explain these facts with a rate concept by assuming that the rate of differentiation of the vertebrae is decisive. For example, in all men a thirteenth rib is primarily formed, and the twenty-fifth vertebra is still laid down as a lumbar vertebra. A shift of the rate of differentiation from tail to head makes the *Anlage* of the thirteenth rib concreate with the twentieth vertebra and disappear; a still higher rate may similarly affect the twelfth rib. Correspondingly, the twenty-fifth vertebra is incorporated into the sacrum; and vice versa, a slower rate of differentiation (= concreation) will leave the *Anlagen* free. In a general way, it is thus possible to account for the facts without assuming special localized actions. In addition, some phylogenetic facts may be reduced to as simple a thing as rate differences (see also page 211).

4. SOME SPECIAL TYPES OF MUTANT GENES AND GENIC ACTIONS

The elementary facts that have been reported thus far are being supplemented by a considerable body of evidence which has been obtained in the study of special cases of behavior of genes and of their action. This evidence will be presented in the present chapter.

A. PLEIOTROPY

This term is frequently used to describe the fact that a given mutant gene produces not only a single change, the one that is usually attributed to it, *e.g.*, vestigial wing, white eyes, but also a number of different phenotypic changes, the number of which

usually increases with more intimate knowledge. We may consider a few examples. The vestigial gene in *Drosophila* produces as its main effect the typical reduced wing. But it also causes the scutellar bristles to point forward and upward, prolongs the time of development, decreases viability, makes wings divergent, and causes rudimentation of balancers. The gene for red eyes in the flour moth simultaneously makes the testes colorless, the skin of caterpillars pale, the optic ganglia red instead of brown, the ocelli of the larvae less pigmented, and decreases the speed of development and the vitality. Numerous examples of this type may be given, some of which we shall discuss in relation to special problems. These effects are usually described as a consequence of the fact that any character is controlled by all of the genes and that only the relative effect of one gene may be larger in a given case, thus making it possible to attribute one major effect to one gene. Such a statement may be correct, but it is not necessarily so. This depends completely upon the developmental process which is changed by a mutant gene and upon the time of incidence of this process. If, for example, a mutant gene like *vgⁿⁱ* produces a deficiency of some growth substance toward the end of development of the *Drosophila* wing, no other effects may occur, or only such simultaneous or later differentiations may be affected as are dependent upon the quantity of the same substance (if any). If, however, the allele *vg^{Nw}* produces a similar deficiency at an early stage of differentiation of the wing disk, it is very likely that other processes of growth that are intimately correlated with imaginal disk differentiation at that stage will be influenced, too, resulting in slower development, diminished viability, and eventual morphological consequences. One of the latter can actually be shown to be a mechanical consequence of the disturbed growth, *viz.*, the upright position of the scutellar bristles. It frequently occurs as a nonheritable abnormality that the two halves of the notum (which are partly developed within the same disk as the wings) do not coneresce properly. In such cases, the scutellar bristles may assume the same position as in vestigial, showing that this position is a consequence of certain mechanical conditions during conerescence. In vestigial flies, such disturbances are more frequent than in Wild stock, and it may be regarded as extremely probable that the bristle character is nothing but

a mechanical consequence of the disturbance of the process of concrescence, produced by the undersize of the wing-forming part of the imaginal disk. A still earlier onset of the pathological process would, of course, have still more consequences; in this case, they are not visible because such forms (homozygous No-wing) cannot develop at all—are lethal.

The working of this interpretation may be exemplified by considering Table 7. Mohr (1932) compared these manifold effects of the *vg*-gene in a series of allelomorphs and compounds. (We must keep in mind that the increasing effect upon the wing was proved to be the consequence of an earlier onset of the destructive process.)

TABLE 7
(Extracted from Mohr)

Wing	Ab- sent	Stumps	Ant- lered	Rag- ged	Scal- loped	Notched	Nicked	Nor- mal
Per cent incisions.....	100	100	100	100	70.7	42.4	27-0.2	0
Divergent.....	++	++	+	+-	-	-	-	-
Erect scutellars.....	++	++	+	+-	-	-	-	-
Rudimentary balancers...	+++	++	+	+-	-	-	-	-

It should be added that time of development and viability would give the same seriation of the effects, increasing with earlier onset of the abnormality. We shall soon have to discuss the same facts again.

There is also available some material in plants that leads to the same conclusions. Anderson and de Winton (1935) found in *Primula sinensis* that genes affecting the organs of the earlier vegetative period (leaves) also affected flowers but not vice versa. If by another mutant gene bracts became leafy, genes acting in the vegetative phase also affected those bracts. Normal bracts, however, react as bracts. Further examples of the same type of action are given, though it is not clear how different types of action upon different organs may be caused by a single genic product.

This rule, that the pleiotropic effect is proportional, *ceteris paribus*, to the earliness of onset of the gene-controlled change in development, may also be illustrated from the cases of mon-

strosities in vertebrates which we studied before. But it must be kept in mind that this time element is not the only cause of pleiotropic gene effects. If the direct action of a gene consists in the production of a substance acting like a hormone, this may affect development all over the body. If the primary effect is of a strictly localized type, nothing else may be affected, except perhaps readjustments in the growth of neighboring parts. Many intermediate and similar cases may be worked out theoretically or be derived from the study of the embryology of mutants. The details will differ in the various cases. But it will always be found that the so-called *pleiotropic effect* of a gene is not a property of the gene and not a general property of gene action but an embryological consequence of the time, place, and type of the primary disturbance of development by the mutant gene.

This explains also why the different characters controlled by a mutant pleiotropic gene may show very different reactions. An extreme case of this type has been reported by Eker (1935). The recessive mutant short wing in *Drosophila* produces small and rough eyes, short wings, scalloping, abnormal venation. These characters have a strange relation to temperature: At 31°, the viability is zero and increases with lower temperature. The phenotypic expression of the traits is 100 per cent at 27.5° and decreases to zero at 14°. (Of course, many cases are known of the dependence of phenotypic expression upon temperature or moisture.) But in addition the different traits have a different temperature-sensitive period—some during the whole of development; others, only at a definite stage. (This case might, however, turn out not to be the result of a simple gene mutation.)

B. MULTIPLE ALLELES

The phenomenon of multiple allelomorphism, discovered by the early Mendelian scholars, has always played an important role in the study of gene action, since the *Drosophila* workers proved that series of multiple allelomorphs are situated at the same locus of the chromosome and therefore may be conceived as different conditions of the same gene, whatever this may mean. As far as I know, Wright (1916) and Goldschmidt (1916*b*, 1917*d*) were the first to derive from the study of such a phenomenon general ideas about the type of action of the gene. According to Wright,

the action of the albino series of alleles in the guinea pig is to be explained on the basis of four quantitative gradations of one factor, which determines the amount of the basic color-producing enzyme. This is produced at a definite rate and acts only above a certain threshold. Here, then, the conception of rate and threshold and of quantitative gradations is applied to explain the details of a case of multiple alleles (see page 88).

Goldschmidt, as described on page 52, studied a series of allelomorphs controlling pigmentation in caterpillars. He could follow these effects through development and found that pigment is developed in different velocities in the different genotypes, which could be characterized by their typical curve of pigmentation. From this it was concluded that multiple allelomorphs act by controlling different rates of one and the same reaction. The same view was simultaneously derived for the action of a series of multiple allelomorphs of the sex genes. In this chapter, we are not concerned with the conclusions upon the nature of multiple allelomorphs but only with the problem of gene action. We have already mentioned a number of cases in which the effects of a series of multiple allelomorphs could be described in such terms, *e.g.*, the vestigial series. *A priori*, such a description will be expected to apply only to those cases—the majority—in which a series of multiple alleles produces an orderly series of graded effects. Whether other types of multiple alleles exist and whether their action has to be understood on a different basis is another question, which we shall take up later.

If we try to discern the different possibilities as to how a series of alleles may control a graded series of effects in an orderly way, we have to realize that a series of reactions of different velocities may act upon development in various ways, which have already been discussed. If, for example, a case of pigmentation is involved, a series of reactions of different velocities may lead to a correspondingly graded series of effects:

1. By controlling the quantity of pigment formed. This may be accomplished: (a) by the amount of chromogen to be oxydized; (b) by the rate and degree of oxidation (or eventually reduction); (c) by the control of the time of onset of one or the other or both of these processes; (d) by the control of the time of the ending of them; (e) by controlling the time from which or during which the organ or group of cells is ready to receive the pigment or its

ingredients; (f) by controlling the threshold above which one or the other of these variables is effective.

2. By controlling the method of diffusion of the ingredients of pigmentation over the organ, which will show different grades of a pigment pattern: (a) by controlling the time of onset and the time of flow of the stream (see pattern, page 193); (b) by controlling some process in the substratum which checks or enhances this flow.

It is not claimed that these are all possibilities. But if one of them is realized here and another there, certainly a number of different types of reactions are imaginable which may lead to graded effects by change of rate. This example for pigmentation may easily be varied to fit cases of growth pattern, of production of bristle-forming substance, or of whatever morphogenetic processes capable of a linear quantitative variation are imaginable.

In a former chapter, we have already mentioned cases of multiple allelomorphs which fulfill all the conditions of an explanation by the concept of reactions of different velocities. We point especially to the case of the vestigial wing in *Drosophila*, where the different indications for this type of action of the genic series were presented as follows:

1. The orderly arrangement of the effects in a quantitative series which included also the compounds at the proper place.

2. The embryological proof that the actual process involved—destruction of wing area—begins earlier and earlier in the increasing series.

3. The fact that at the beginning of the series a typical overlapping with the normal takes place with a regular increase of percentage in the ascending series.

4. The fact that the highest members of the series drift from increasing inviability into lethality.

5. The fact that change of temperature shifts the effect within the same series.

6. That effects of the same type and seriation may be produced as phenocopies by temperature shocks or X rays.

7. That effects of modifying genes may produce the same shifts.

8. That certain phenomena of symmetry fit into the general type of explanation (see page 229).

Another type of series already mentioned, which presented facts that could be conceived only in terms of different rates of one

reaction, were cases of pigmentation in guinea pigs or *Drosophila* eyes. Numerous similar examples are found in genetic literature (see Stern, monograph, 1930), which all lend themselves to the same type of interpretation.

The next point to be considered is the action of pleiotropic genes in such series. One and the same gene, in different multiple allelomorphous conditions, acts upon many phenotypic characters, and this may be done by changing the rate of one chain of reactions which affects a developmental process, thus leading automatically to manifold effects (see foregoing chapter). In this case, the different characters affected ought to show corresponding series of gradations, provided this is possible. (This restriction means that the development of an individual trait might be of an all-or-none type, which would exclude intermediate steps.) It must be kept in mind, however, that such an expected parallelism need not be of the simple type of simultaneous and parallel change of each character. Let us take an example. A series of effects may be produced by an earlier and earlier onset of some process, as in the vestigial case. As embryonic development consists of a series of determinative processes which narrow down the potentialities of parts of the embryo, an earlier onset of a change will affect more potentialities. If we take the vestigial case, it is a fact that the imaginal disk for wing formation contains also a thoracic bud and that these two areas are separated only during development. Let us assume that a series of earlier and earlier changes occur in the wing *Anlage* in the imaginal disk. They will affect only the wing down to the stage at which determination of wing and thorax *Anlage* occurs. At an even earlier stage, however, the still equipotential *Anlage* is affected, and the resulting change occurs in both wing and thorax. The latter effect then will appear in the series only near its highest point. This example shows that in a given case the same reaction might lead to effects in different organs which might begin at different levels of the series. It will be easy to imagine manifold variations of this one example. The following diagram represents three such possibilities of pleiotropic effects upon the three characters *A B C*, caused by a series of allelomorphs n^1 , n^2 , etc., all resulting from one and the same reaction, which hits different embryological processes at different levels.

DIAGRAM

Character	Phenotypic expression grade 1 to 5 in the multiple allelo-morphic series n^1 to n^5				
	n^1	n^2	n^3	n^4	n^5
<i>A</i>	5	4	3	2	1
<i>B</i>	5	4	3	2	1
<i>C</i>	5	4	3	2	1

or

<i>A</i>	5	4	3	2	1
<i>B</i>	3	2	1		
<i>C</i>	2	1			

or

<i>A</i>	5	4	3	2	1
<i>B</i>	2	1			
<i>C</i>	1				

or

in the case of an all-or-none response of character *C*:

<i>A</i>	5	4	3	2	1
<i>B</i>	5	4	3	2	1
<i>C</i>	5	5	5		

In the section on pleiotropy, we have given an example, the vestigial series, corresponding to the second diagram. Other cases of such parallel effects, with or without shift between the characters, are found in genetic literature. Here are a few examples taken from Stern's monograph in table form:

TABLE 8
(Compiled from Stern's Monograph)
Dichaete Alleles in *Drosophila*

	Bristles	Wings
+	Normal	Normal
D^e	Normal	Variable
D^3	Almost normal	Spread
<i>D</i>	Absent	Spread

TABLE 8.—(Continued)
Pharbitis Nil, the maple alleles (Imai)

	Leaves	Corolla	Fertility
<i>M</i>	Normal	Normal	Normal
<i>m</i>	Maple	Partly split	Normal
<i>M^w</i>	Willow	Split	Female sterile

Drosophila obscura, white alleles (Lancefield)

	Eye Color	Testis Color	Vitality
+	Red	Orange	Good
<i>w^e</i>	Eosin	Colorless	Medium
<i>w</i>	White	Colorless	Poor

Drosophila willistoni deformed series (Lancefield)

	Eye Surface	Bristles	Hairs	Scutellum	Wings	Vena- tion
+	Normal	Normal	Normal	Normal	Normal	Normal
<i>d^s</i>	Rough	Almost normal	± Chubby	± Normal	± Spread	Normal
<i>d</i>	Rough	Bent	Chubby	Round	Spread	Defect

Drosophila melanogaster, lozenge eye

	Smooth cornea	Fertility
+	Normal	Fertile
<i>lz⁴</i>	Increasing smoothness	Fertile
<i>lz¹</i>	Increasing smoothness	Sterile
<i>lz²</i>	Increasing smoothness	Sterile
<i>lz⁵</i>	Increasing smoothness	Sterile
<i>lz³</i>	Increasing smoothness	Sterile

Rabbit, Russian pattern series (Kosswig)

	Yellow pigment	Black pigment	Eye pigment
C self	Present	Present	Present
<i>C^{ch}</i> chinchilla	Almost absent	Present (?)	Present
<i>C^d</i> dilute chinch.	Almost absent	Reduced	Reduced
<i>C^m</i> sable	Almost absent	More reduced	Much reduced
<i>C^r</i> russian	Absent	Only at tips	Absent
C albino	Absent	Absent	Absent

Many more variations are imaginable, all of which may be explained by the action of a single process occurring at different rates. There is an interesting fact to be mentioned in this respect. We remember that most of the mutant characters of *Drosophila*, including also multiple-allelomorphic series, could be reproduced as phenocopies. Some such cases involved effects which in the case of the actual mutant show pleiotropic phenomena. Thus the series of the truncate genes in *Drosophila* affects the wing in the series oblique—dumpy—truncate but affects simultaneously the hairs on the thorax, which form a vortex in different degrees. In Goldschmidt's experiments on phenocopies, the types of the wing series up to dumpy could be reproduced, but there was no vortex. This shows that the hair character has a different sensitive period to temperature shocks; *i.e.*, different details of developmental procedure are involved. (See the facts regarding different sensitive periods in pleiotropic characters of the flour moth, page 246.) This agrees with the facts on pleiotropic multiple allelomorphs and their explanation.

There is another set of cases in which some of the characters controlled by the allelomorphic series show parallel seriation whereas others do not. To this belongs also the vestigial series which we tabulated on page 80. In this table, we omitted another trait, found by Mohr (1932), *viz.*, a shortening of the second wing vein which is observable in the medium and lower members of the series. This character does not follow the same seriation as the others. If we use the same arrangement of the *vg*-series as in Table 7 (page 80), the percentage incidence of the character in question seems haphazard: 100, 2.1, 100, 0, 8.8, 73.3, 0, 2.6. If we look at the details of Mohr's data, however, we find a rule: The three high percentages are the compounds in which the No-wing allele is involved. No-wing has also other peculiarities, for it is semidominant to Wild type and is homozygous lethal. From this one might draw the conclusion that here some special feature is involved which we do not understand yet but which has nothing to do with the general chain of reactions involved in the series.

The oldest and best analyzed example of this type is Wright's analysis of the albino series in guinea pigs (1916, 1925). Here a series of multiple alleles produces a progressive dilution of pigmentation down to albinism. If the gene for black color is

present, the effect ranges from black over sepia to white; if red is involved, it is shifted over yellow to white. Simultaneously, the eye color is affected, ranging from black via red to pink. These three series of effects, however, are not strictly parallel, as the following table (after Wright, 1925) shows. In this table, the colorimetric values for intensities of dark pigment are assembled:

TABLE 9
(After Wright)

Allele	With black	With yellow	Eye color
<i>C</i>	14	10.6	Black
<i>C^kC^k</i>	13.1	7.1	Black
<i>C^dC^d</i>	9.9	7.0	Black
<i>C^rC^r</i>	13.1	0	Dark red
<i>C^aC^a</i>	0	0	Pink (no pigment)

The table also shows that the seriation is parallel for yellow pigment and eye color but not parallel for those in the black-pigment series. Wright discusses these facts in a way that ought to have settled the argument. There are two possibilities. Either the black and yellow pigmentations are due to different processes in development, in which case there is no reason why any correlation ought to exist, and there is no problem at all. Or the albino series affects primarily one and the same reaction of pigment formation. In this case, the discrepancies of the effect in the different series are due to developmental processes subsequent to the effect of the albino factors. Wright thinks (1916, 1925) that it is mainly a threshold problem, *viz.*, that the threshold for yellow is higher than that for black. "The red-eyed dilutes may have a great deal of black in the fur but no yellow. The typically yellow parts of the tortoise-shell or the agouti patterns are represented by pure white. Even albinos develop black in the ears, nose, feet . . . but never a trace of yellow." Similar facts are known for other rodents (see Wright, 1925). Wright shows that the available data reveal the same situation in six mammals, pointing to a general rule regarding threshold differences between black and yellow. We shall return to the same facts in the chapter on dominance and also in the chapter on the theory of the gene.

This discussion touches the decisive points (if we leave out of account here the reflections upon the nature of the genes involved). (1) Facts of this type are expected if different processes are involved. (2) If one process is involved, any special feature of a developmental process that is in some way connected with the main process will result in such phenomena as are discussed here. Such developmental variation may depend on the control of a threshold, but it may also be conceived in many different ways. Most cases of this type have been reviewed in Stern's Monograph. If we consider them from the standpoint of Wright's discussion, there will be no difficulty in reducing the discrepancies of seriation to such interferences as different thresholds, all-or-none effects for certain processes, or changes of general situations of development in an orderly way, such changes interfering only with the differentiation of one organ (see the discussion in Goldschmidt, 1927c). Probably most frequent are those cases in which the time relations of development (order of growth, etc.) are different in different organs and the alleles affect some process at a definite time. Let us assume A, B, C, D to be successive points in development at which the alleles m^1, m^2, m^3, m^4 act. One action determines the quantity of pigment in a linear series proportional to the time of onset (A, B, C, D) of the reaction controlled by the alleles. Another consequence of these reactions would be an influence upon the growth of another organ, say speeding up growth. If, now, the normal growth of this part should occur at the times A, B, C, D in the following seriation: grow thin breadth/growth in length, growth in length, growth in breadth, then the alleles m^1, m^2, m^3, m^4 would produce the following seriation of the length-breadth index in favor of length: $- + + -, i.e.,$ a different seriation from the pigment series. This model, which might be varied in many ways (see Goldschmidt, 1932a, 1933c), allows for all cases of not parallel pleiotropic action of multiple alleles, without changing the general interpretation that such genic series control different rates of one primary reaction.

Whether there are cases of multiple allelomorphs that act in such an irregular way that no simple explanation is forthcoming is another question. Many such cases are known, and they are reviewed in Stern's monograph. Some of those may be brought in line when the actual facts of development are known. Others may turn out to belong to a different category of facts; and,

again, others may defy a simple explanation. This, however, would not change the fact that most multiple-allelomorphic series give definite information regarding the action of the respective genes upon development. More facts will be presented in other chapters.

C. GENES CONTROLLING KNOWN CHEMICAL PROCESSES

The effect of a genic action may be a morphogenetic process of any kind; it may also be the production of a physiological condition; and it may be the final production of a definite chemical substance deposited somewhere in the body. In general terms, we might assume that all genes act primarily in the same way. The different types of end effects will therefore probably furnish no different clues in regard to the primary reactions set in motion by the genes. But there is a long chain of processes leading from the gene to the final phenotypic expression of its activity. When morphogenetic processes are involved, usually the members of the chain that may be unraveled (see later chapter) cannot be defined chemically but only in such general terms as growth substances, evocators, hormones of differentiation. If, however, the end of the chain is a definite chemical situation, there might be the possibility of finding some members of the chain and of defining actions of mutant genes in terms of definite chemical processes.

Strictly speaking, all the processes of deposition of pigments in eyes, hairs, feathers, skin, many of which have already been mentioned, belong here. But in most cases, these processes have been studied only in a rather general way from the standpoint of chemistry. In certain cases, it is known whether melanin pigments are involved or pigments of the carotinoid type, whether different pigments may be different grades of oxidation or reduction of one substance, and similar rather general facts. Such cases have been mentioned, and the fact was noted that the phenotypic result might be dependent upon time or quantity of formation of the chromogen (tyrosin, etc.) or similar quantitative variants of the action of the catalyst (dopa, oxidase) or both. More examples will be discussed later on. But as a rule the chemical elements of these processes could not be clearly defined (see page 91).

There are, however, a few actual chemical attacks on these problems in animal genetics.

The first Mendelian studies of animal pigmentation tried to explain facts in chemical terms. Cuénot (1902, 1911) assumed that albinos do not contain chromogens but oxidizing enzymes. Later, Gortner (1910–1913) showed that the color varieties of the potato beetle contained different amounts of chromogen in the elytra. Onslow (1915), on the other hand, found that in rabbits the main differences are not due to the chromogen but to the enzyme component. He actually found peroxidases in the skins of gray, black, and brown rabbits, which oxidize tyrosin to melanin in the presence of hydrogen peroxide. In all recessive white skins or parts of skins, he found the peroxidase missing, though the chromogen was available; and in the dominant white English, an antityrosinase prevents melanin formation. The same was found in the belly of light-bellied pigmented forms. In yellows, no peroxidase was found.

Koller (1930) repeated the tests with the same results and added that a pigmentation inhibiting extract from dominant white does not act upon dominant black. (It ought to be added that the relation found here cannot be generalized. In other cases, genes for no or less pigment might control the chromogen part of the reaction.) Wright (1916) used these facts—also certain assumptions made by Little (1913)—to give a general explanation of gene action in regard to coat color in chemical terms. There is a basic color-producing enzyme (I) which acting alone on chromogen produces a diffuse pigment which appears yellow. The albino series of alleles produces this rather unstable enzyme at different rates (see page 88). There is another enzyme (also an oxidase) II, which stabilizes I and makes it oxidize a chromogen into the coarser pigment granules of dark pigmentation. I and II together set the threshold for action of I at a lower level. The rate of II controls the admixture of dark to yellow pigment in the different color types. More details will be found later. Here belongs also the work of Schultz (1935) on eye color of *Drosophila* which has been discussed.

The same problem has been attacked by Graubard (1933) for pigment races in *Drosophila*. He tried to compare the tyrosinase content of yellow, wild, black, and ebony flies. To do this he devised methods for estimating the enzyme concentration, *ceteris paribus*. The results were very strange. Different

results were obtained for larvae, pupae, and flies, also different results for different treatments. For example, sometimes living larvae yielded little or no enzyme, which was increased after addition of chloroform or after grinding the tissues with sand. Young flies did not yield any enzyme at all. Graubard concludes that the enzyme concentration may be of no importance at all for melanin formation but that the decisive action rests with the internal environment, which controls how much of the enzyme may take part in the reaction. Another fact seems to corroborate this. Extracts prepared under the same conditions may contain tyrosinase in the following diminishing order for the races tested:

1. In pupae: yellow, wild, black, ebony.
2. In larvae: yellow, black, wild, ebony.

Graubard concludes, therefore, "that it is certain that Goldschmidt's picture of the gene-enzyme end-result relationship is far too simplified." It seems doubtful whether this analysis lends itself to reliable conclusions upon the genic action.

1. It is not necessarily the enzyme that is supposed to vary in concentration; it might also be the chromogen.

2. The variable might be neither enzyme nor chromogen but the time of onset or of ending of the oxidation process.

3. A measurement of the oxidase content of the whole animal may be irrelevant for the happenings in the cells or organs that deposit the pigment.

4. Methods that do not permit the discovery of any enzyme in the young fly before darkening can hardly be called sufficiently quantitative to permit of conclusions.

5. The assumed inhibiting action of the internal environment may be identical with the selective distribution of the enzyme to the regions of action.

In this connection, we must consider the work of Schmalfuss and Werner (1926) who attacked the problem as chemists in model experiments. They used as a chromogen an amino acid (1- β -3,4-dioxyphenyl- α -amino propionic acid) and as oxidase a ferment from the blood of caterpillars. The blood was soaked into strips of filter paper and dried. Chromogen was added to these strips, and pigment formation occurred; the conditions of pigmentation were then studied. It was first found that melanin formation depends upon the pH. Acids interfere with the action

of the oxidase; bases, except in high concentration, increase the rapidity of melanin formation. There is no influence of light, and a considerable one of temperature. This seems dependent mostly upon the presence of a second catalyzer which is heatproof. Systematically all types of substances were studied in regard to their action upon melanin formation; some of them enhanced it, while others interfered in different quantitative degrees (grades from light grey through brown to black), which were measured. Certain chemical rules were found, but these do not mean much for the genetical analysis. The only conclusion that is warranted is that, given chromogen and ferment, the amount and color of pigment may depend upon a number of chemical conditions which might be produced by other genes controlling them.

More suitable material is found in plants, because here the basic chemistry of the pigments is thoroughly known after the work of Wheldale, Willstaetter, Robinson, Karrer, and others. Most of the work relating mutant genes to actual chemical products has been done by Euler and his collaborators on the one hand and the collaborators of J. B. S. Haldane (see 1935) on the other, after the pioneer work of Miss Wheldale (later M. W. Onslow) in early Mendelian days (see Onslow-Wheldale, 2d ed., 1925).

Euler and his collaborators studied in a long series of papers (Euler *et al.*, 1929-1935) the chemistry of chlorophyll-defective mutants of barley, which had been genetically analyzed by Nilson-Ehle and Hallquist. The results were checked with similar mutations in other plants. There are the completely white albino types of which seven genetically different ones were tested; also the yellowish xantha and the pale alboxantha types. The chemical differences between these types were analyzed. The main results thus far are:

1. No chlorophyll whatsoever is present in the albino forms. The heterozygotes, however, have normal chlorophyll content and complete dominance.

2. The base of chlorophyll is the porphyrin-nucleus which contains about 70 per cent of the mass of the molecule. The white mutants produce only a small amount of porphyrin, indicating that the disturbance occurs earlier than the porphyrin synthesis. Carotin synthesis, which is chemically related, suffers in the same way.

3. The content of katalase in the white mutants is reduced to about one-third the normal amount. In the cotyledon, it is still normal.

4. In two of the albino lines but not in the others, also not in colored lines, a methylated Indolyl base was found, indicating specific chemical activities.

5. In albino forms, the plastids are defective; less so in the xantha. This points to the possibility that the primary effect of the mutant gene is upon the plastids. In this case, the gene would not be concerned directly with chlorophyll synthesis, and the facts would not help much to understand the chemical side of gene activity.

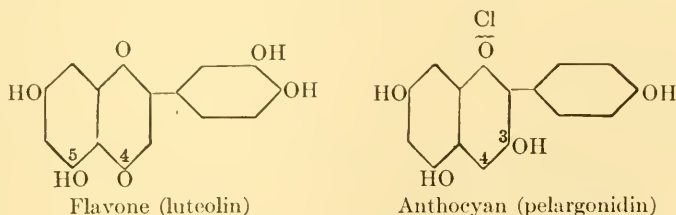
Before reporting upon the best analyzed case, flower color, we shall mention a piece of work that is of a more physiological than strictly chemical type, Brink's (1929*a, b*) studies on the waxy gene of maize. This recessive gene produces among other effects the presence of a specific type of reserve starch in the male gametophyte, the pollen grain. As this gene segregates in the pollen tetrad, the chain of reaction between the gene and its effect is no longer than the time of the reduction division. Chemically the two starches are very much alike as far as the basic sugar is concerned, but Brink found that certain differences in reactivity pointed to a structural difference. This seems to have to do with the amylase, as extracts from waxy pollen give a lower curve for glucose production than extracts from normal grains, *i.e.*, show a higher diastatic activity. Brink concludes from this that the amylases in both cases may be different in kind and therefore attributes to the mutant waxy gene the ability to produce a somewhat different diastatic enzyme.

It is not necessary here to go deeply into the chemistry of flower colors. Only such facts will be mentioned as seem to be important from the standpoint of gene action. We shall follow mainly the most recent work in the field by Miss Scott-Moncrieff (1936). Flower color may be determined by a number of agencies. If one pigment is involved, the color depends upon the pigment in question and also frequently upon the pH of the milieu. If more than one pigment is involved, different possibilities are given as follows:

1. There might be a combination effect.

2. There might be a background effect (just as in many animal colors, *e.g.*, the skin of a tree frog; of course no pigment cells are involved in plants).

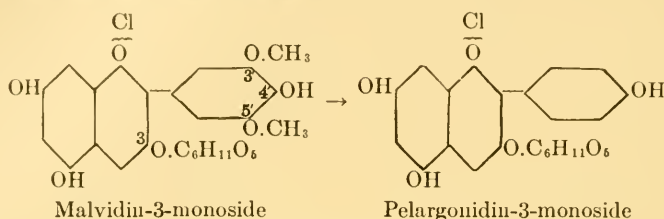
3. There might be the so-called copigment effect, which means that a certain type of pigment is changed in color by the mere presence of another pigment. The pigments involved are (a) the plastid ones, carotin and xanthophyll; (b) the more important sap pigments. The latter fall into two main groups, the anthoxanthins and the anthocyanins. The xanthins have ivory to yellow color and belong chemically to the group of flavones. They may or may not occur as glucosides (containing a sugar residue). They may produce independent color effects, act with a background effect, act as copigments or quantitatively together with the anthocyanins. Their genetic relation to the anthocyanins will be discussed later. As copigments they have a bluing effect upon anthocyanin. The anthocyanin pigments are sap-soluble glucosides which vary in color from scarlet through violet and purple to blue. Generally, their structure is similar to that of the xanthins, the fundamental differences being the substitution of an O-atom at position 4 in the flavones, as shown below.



They fall into three main groups: pelargonidin, cyanidin, and delphinidin types, differing by the possession of 1, 2, or 3 OH-groups on the side phenyl ring (the preceding formula has one and is a pelargonidin). More than one of these pigments may be present in a plant, and there are numerous chemical variations such as methylation of one or more OH-groups, changes in the sugar residue, and addition of an organic acid. These variations and substitutions are caused by genetic factors. Most important are the sugar residues situated at position 3 or 5. These might be glucose, galactose, cellobiose, and others; *e.g.*, pelargonin.

cyanin, peonin, petunin, malvin, and delphin are all 3-5 glycosides respectively of the pelargonidin, etc.

Mutations in flower color may be based on the different possible changes in regard to the anthocyanin formula, the copigment, and the pH. The chemical change may be of many different types. By way of illustration, we mention only a single type, where the mutated gene prevents the methylation of the complex, as shown below:



The following extract from Scott-Moncrieff's table for *Primula sinensis* indicates some of the different types of action of some of the genes. Wild type is magenta by malvidin-3-monogalactaside (primulin) copigmented by anthoxanthin (pH 5.3).

TABLE 10
(From Scott-Moncrieff)

Gene	Action on flower color	Appearance, pigmentation, and pH of mutant
<i>K</i>	Modifies general anthocyanin substrate to more intense 3.5 oxidized and methylated type	Pale coral or white pelargonidin 3-monoside pH 5.3
<i>B</i>	Produces anthoxanthin, copigmenting and suppressing of anthocyanin	Red; primulin, no anthoxanthin pH 6.0
<i>R</i>	Produces localized acid pH in the petals and in the red corolla tubes of <i>p</i> and <i>g</i> forms	Blue; primulin and anthoxanthin (pH 6.0)
<i>D₂</i>	Produces specific anthocyanin-pelargonidin 3-monoside	Bright magenta; mixture of primulin and pelargonidin 3-monoside pH 5.3
<i>G</i>	Inhibits anthocyanin in flower center and together with <i>D</i> inhibits the effect of <i>R</i> in petals. Inhibits anthocyanin and the effect of <i>R</i> in tubes	Red stigma, dark center; pH 5.3 red tubes pH 5.6

In a similar way, a considerable number of plants with known genetic basis have been analyzed by Wheldale (Onslow), Robinson, Lawrence, Hagiwara, Shriner and Anderson, Sando, Milner and Sherman, and Scott-Moncrieff (1936). They have been reviewed by this last investigator. From all the available material Scott-Moncrieff derives some general information regarding flower-color variation: In some cases, the action of the different genes is independent and additive; in others, an interaction is found or a dependence of the effect upon the pH. The following list covers the majority of known types of gene action:

A. CHEMICAL CHANGES OF ANTHOCYANIN

1. Oxidation of the aglycone (without sugar residue) at 3' or 3' and 5'.
2. Oxidation and methylation at *ibidem*.
3. Methylation of the aglycone at *ibidem*.
4. Glycosidic change from 3 to 3-5 type.
5. Acylation.

B. SAP-PIGMENT PRODUCTION

1. Anthoxanthin and anthocyanin.
2. Yellow anthoxanthin background and interaction effects.
3. Ivory anthoxanthin copigment interaction and copigment effects.
4. General anthocyanin background and interaction effects.
5. Specific anthocyanin background and interaction effects.

C. SAP-PIGMENT REGULATION

1. General intensification.
2. General suppression.
3. Local intensification.
4. Local suppression.

D. PLASTID PIGMENT

1. Production background effects.
2. Inhibition.

E. LOCALIZED ACID PH

Table 11 shows a few examples of such actions.

The problem is now to find the general rules that might be deduced from such facts. We leave out of consideration here the different interactions and localized effects, as these are problems of pattern formation and not directly concerned with genic action; partly they are also problems of genic interaction to which we shall return soon. One of the general results of such studies

is that the genes in question exercise a highly specific action upon such synthetic chemical processes as oxidation, methylation, addition of sugar or acid residues at definite locations, and control of pH, in addition to the production of a more generalized basic substance. Another point may be derived from the fact that in many of the cases the Wild-type color is the most highly oxidized one; mutant genes then prevent complete oxidation, which again may work by controlling the rates of a decisive process which might have to do with the specific catalyst involved in the reaction. But, as Haldane (1935) remarks, it is very difficult to draw definite conclusions upon the action of a gene from such facts. "The gene which is responsible for the methylation of a certain hydroxyl may be itself a diastase, may produce one, or may be concerned with a reaction which liberates the necessary energy for the action of an already present diastase." But, in a general way, Haldane, like many others, assumes that the action of the gene results, in most cases like those which were mentioned, in the production of a specific catalyst.

TABLE 11
(After Scott-Monerieff)

Examples of gene action	Varieties		
	Dominant	Recessive	Gene
I. Yellow plastids: <i>Cheiranthus cheiri</i>	Yellow	Lemon	<i>Y</i>
II. Yellow anthoxanthin: <i>Antirrhinum majus</i>	Yellow	White	<i>Y</i>
III. Ivory anthoxanthin copigment: <i>Primula sinensis</i>	Magenta	Red	<i>B</i>
IV. General anthocyanin: <i>Dahlia variabilis</i>	Scarlet	Yellow	<i>B</i>
V. Specific anthocyanin: <i>Papaver Rhoeas</i>	Scarlet	Pink	<i>T</i>
VI. Oxidation of anthocyanin aglycone. <i>Antirrhinum majus</i> (3-rhamnoglucosides).....	<i>Cyanidin</i> Magenta	<i>Pelargonidin</i> Red	<i>B</i>
VII. Oxidation and methylation of anthocyanin.....	<i>Malvidin</i> Pink	<i>Pelargonidin</i> Salmon	<i>X</i>
VIII. Local change in pH: <i>Primula sinensis</i>	Magenta	Blue	<i>R</i>

A special type of genic action controlling definite chemical processes is, finally, the production of the stuffs that are responsible for serological specificities. The bodies that make for the blood-group differences belong here. A recent study by Abderhalden (1936) has revealed another group. Rabbits injected with proteins from other animals produce proteinases which specifically split those proteins and which may be isolated from the rabbits' serum. By aid of the specificity of these enzymes Abderhalden demonstrated protein differences between different lines of guinea pigs, distinguished by single genes. If this should be confirmed, it might lead to interesting conclusions.

5. THE GENE IN HETEROZYGOUS STATE

Since early Mendelian days, it has generally been assumed that the phenomenon of dominance must one day lead to an insight into the nature of the gene. Correspondingly, it was assumed that dominance or recessiveness were attributes of individual genes. Bateson, as is known, believed that dominance is the presence and recessiveness the absence of the thing called a gene, an idea that, however, was refuted at the outset by Correns' (1899) discovery of dominance of two recessive genes over one dominant in the triploid endosperm of maize. Later dominance was attributed to different potencies of the genes (Davenport, 1908; Kellogg, 1908), which might change even individually. Only slowly geneticists began to realize that dominance is not a property of the gene but of the phenotype. It seems that Tower (1910) was the first to report that dominance could be changed at will in the same heterozygote of *Leptinotarsa undecimlineata signaticollis* by proper control of temperature and moisture. At about this time, some geneticists realized that dominance was not a property of the gene but something "floating, capable of being shifted," as Goldschmidt expressed it in the first edition of his textbook (1911a).

As far as I know, the first trial to express dominance in terms of development was made by Goldschmidt (1916c, 1917c), when he found that a case of so-called change of dominance during development had to be explained by the respective velocities of processes of progressing pigmentation. Dominance then was controlled by certain time relations of processes or reactions occurring during development which could be expressed in a

general way by the words: The faster reaction wins the race. The further development of genetical knowledge, especially of the interaction of genes, the action of so-called modifiers, led to a general recognition of the idea that dominance is not a property of the gene but a phenotypic result of the action of the gene in connection with other gene-controlled developmental processes or environmental actions. Wright (1925), in connection with the fact that the Wild-type gene C is dominant over all members of the albino series, designated such a process a threshold effect, controlled by other genes. A generalized theory of

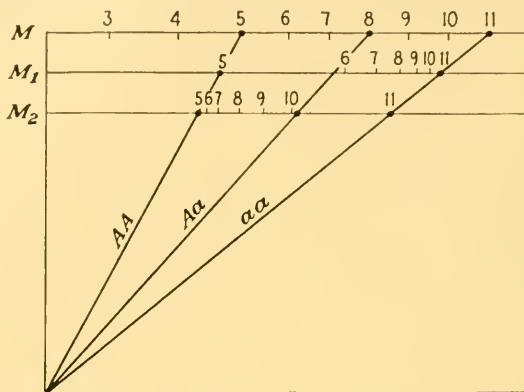


FIG. 23.—Diagrammatic representation of dominance relations if the number of cell divisions determines the phenotype, if and the effect of the heterozygote is intermediate between that of the homozygotes. M , M_1 , M_2 are different systems of incidence of cell division. (From Goldschmidt, 1927. *Phys. Th. d. Ver.*)

dominance as a phenomenon of development was developed by Goldschmidt (1927c), who explained the phenomenon as a necessary consequence of the type of action of the gene in controlling development. This theory is still the only one adaptable to all facts and the only one that furnishes the necessary physiological basis to all phylogenetic theories of dominance (see page 121). The following case may serve as a model which might be adapted easily to other cases by changing the respective variables. Let us assume two allelomorphs controlling a character which might be measured in quantitative terms, like the number of facets in an insect eye. The dominant gene controls a reaction of a certain velocity; the recessive allele, a reaction of lower velocity; and the heterozygote, an intermediate reaction (see Fig. 23). The reaction leads to a determining effect when the products have

reached a definite concentration at the level M . For simplicity's sake, we assume that the hereditary character in question is the size of something, controlled by the number of cell divisions. For our model we assume that the reaction in question is one that stops further cell division. If the progress of cell division up to this point is determined independently, the size of the organ will be smaller the earlier the curve reaches the level M . If, now, the cell divisions proceed in equal intervals, the heterozygote Aa will be exactly intermediate between AA and aa . Let us now suppose that the rate of cell division increases with time as marked on line M_1 (the numbers indicate succeeding cell divisions) and that the number of cell divisions alone decides the size of the organ. In this case, in the heterozygote, cell division ceases before six divisions have been completed, and therefore the small size (AA) appears almost completely dominant. (Stopping after five divisions characterizes AA .) If cell divisions proceed faster at first and then slow up (line M_2), almost complete dominance of the large size ($aa = 11$ steps) results. Dominance in this case is then conceived as a function of the following variables: the velocities of reaction controlled by the main gene, the threshold concentration at which this reaction leads to a morphogenetic effect, the type of effect, the numerical system of the independently determined process that is involved. It is clear that this simple model allows for innumerable variations. To mention only one, the reaction A may stop or initiate or slow down or speed up cell division or growth between the divisions. It is clear that this type of model may be easily changed to fit any imaginable gene-controlled process; and of course other variables of a rate type, threshold type, or all-or-none type may be easily added to describe the most different cases.

Wright (1934*d*) has used the same type of reasoning but put more emphasis, as Goldschmidt also originally did, on the rate of reaction catalyzed by the genes in question. This means that, though not neglecting the other variables of our model (Fig. 23), he emphasized specially the rate relations between the products of dominant, heterozygous, and recessive genes, which in our model have been assumed to be of a simple type. Wright's deductions may therefore be added to that model as a further analysis of one of its variables. Wright starts from the neces-

sary assumption that there is a chain of reactions between the gene and the end product and that any condition that makes one link in the chain act in the heterozygotes as it acts in the homozygotes will result in dominance. He assumes that the gene acts as a catalyst controlling the rate of production of some substance (in harmony with Goldschmidt's basic assumptions) by a chain of irreversible transformations, the intermediary substances being in a flux equilibrium. These reactions may be treated as monomolecular and dependent upon the joint concentration of catalyst and substrate. The rate in this case varies directly with the concentration of the catalyst, and the curve expressing the relation of variation in the product with variation in the catalyst is a hyperbole, asymptotic at its upper limit. Therefore with increasing activity of the gene its heterozygous effect ought to approach dominance. Another possibility is that a bimolecular reaction is involved. The general consequences are shown to be the same, though a number of new possibilities appear, *e.g.*, one part of the reaction setting a threshold for another. A third possibility is assumed, *viz.*, that the rate depends not separately on concentration of substrate and enzyme but on their compound. Also, in this case, a similar result will follow, *viz.*, a relation between the difference in the quantity of the catalyst and the amount of dominance. Without going into further details of Wright's calculations, we realize that in his view again dominance is dependent upon the same elementary gene-controlled processes as are involved in the model (Fig. 23), emphasizing more the behavior of the primary chain of reactions. Thus we see that dominance is best conceived as a consequence of the quantitative aspects of genic action and their quantitatively fixed interplay in time and space during development. If this is correct, dominance, vice versa, furnishes important facts toward the understanding of genic action. To these facts we shall turn now.

A. THE INFLUENCE OF THE ENVIRONMENT UPON DOMINANCE

If dominance is controlled by a developmental system, as indicated above, it ought to be possible to shift the phenotype of the heterozygote by environmental action in the same way as the mutant phenotype may be secured as a phenocopy. This is especially to be expected when the mutant phenotype appears

as a simple quantitative deviation from Wild type toward insufficient production of something needed for perfect development. Muller (1932a) has called this type of mutant gene hypomorphic. It is the most frequent type of recessive mutation. We might distinguish two possibilities of such actions. In cases of incomplete dominance, the degree of intermediacy might be shifted experimentally. Or in cases of complete dominance, this might be broken. *A priori*, the former type of effect would be expected to be of general occurrence, being, after all, nothing but a special case of the general type of modification. It is, however, to be expected that the second type of shift is more difficult to accomplish, because complete dominance requires certain threshold conditions (see page 117), with the result that even a considerable shift does not carry the type below the threshold.

Examples for the first group may again be taken from the much studied case of vestigial wings in *Drosophila*. We recall that the *vg*-wing may be changed by temperature action into the phenotypes of all the other alleles. M. H. Harnly and M. L. Harnly (1936) discovered a new allele pennant which has normal or slightly notched wings and reacts strongly to temperature changes in different ways.¹ The heterozygotes with *vg* may show very different types according to the temperature at which they are raised, fluctuating from *vg*-strap type at 26 to almost normal at 32°. Here, then, temperature shifts the heterozygote exactly as it shifts the homozygous *vg*-wing. The explanation in terms of rates is obvious. It must be emphasized that the *vg/+* - heterozygote is usually Wild type in all temperatures (see page 117).

At this point we have to mention a phenomenon that resembles a shift of dominance and has actually been confused with it (see also preceding footnote concerning the same error by Harnly). Hersh and Ward (1932), among others, compared wing length and area in homozygous *+* - flies and the hetero-

¹ M. H. and M. L. Harnly base their results upon measurements of wing areas. This leads to erroneous results, the details of which will therefore not be reported. His data show that the pennant wings are affected by temperature considerably in general size, *i.e.*, in cell growth after differentiation. The measurements then lump together this influence upon secondary growth with the effect upon the scalloping of the wing, which is a different process. Goldschmidt's results in this respect could not have been known to Harnly.

zygous $+/vg$ - flies at different temperatures. In both cases, the wing area decreases with rising temperature. This they treated as a dominance effect and calculated even dominance coefficients. The assumption, of course, was that vestigial produces a small area. As we know now from Goldschmidt's work, the *vg*-effect has nothing to do with wing growth but with destruction of parts of the wing. A wing without notches is therefore completely dominant. If temperature affects the wing area in either homozygotes or heterozygotes, the *vg*-gene is not involved at all but a growth process, primary or secondary (probably only secondary) cell growth. The results therefore have no bearing upon the action of the *vg*-gene or its normal allelomorph but only upon the problem of whether or not the *vg*-heterozygote reacts differently from the Wild type in regard to growth under different temperatures. The small difference actually found may have many causes, which might or might not allow conclusions upon genic action.

The most complete and most thoroughly analyzed data have been presented by Hersh (1930a) for the Bar-eye mutants of *Drosophila*. Here dominance of the Wild type is not complete (the *Drosophila* workers call Bar, therefore, a dominant, a rather inexact but useful way of labeling), and therefore a shift of dominance is to be expected. The number of facets in Wild-type eyes and the eyes of the mutant series is a function of temperature and may therefore be expressed as a curve for the range of this variable. Hersh (1930b) calls such a curve a thermophene. If such thermophenes for Wild type, mutant, and heterozygote were compared, they might be parallel. This would indicate that a general process of growth is involved but not the phenomenon of dominance. If a measure for dominance should be introduced, it would remain inconstant through the range of temperatures. If, however, the curve for the heterozygote should not parallel that for the homozygotes, conclusions upon dominance might be drawn. In this case, an eventual coefficient for dominance would change over the temperature range. Hersh uses Zeleny's (1920) formula for calculating a coefficient of dominance:

$$Co = \frac{AA - AA_1}{AA - A_1A_1} \times 100$$

in which AA and A_1A_1 are the obtained quantities for the character in the two homozygotes and AA_1 in the heterozygote. Instead of using directly the facet counts, he applies a dynamic view by considering the instantaneous addition of facets. He had found before that the rate of change in mean facet number at any temperature is proportional to the mean facet number at that temperature, *i.e.*, an exponential relation of the formula $y = ae^{rt}$, in which r is the relative rate of change, t the temperature (centigrade), e the base of the natural logarithms, and a a constant. The instantaneous change in facet number at a given temperature is then expressed by the first derivative:

$$\frac{dy}{dt} = yr$$

This value he calculates for the different facet numbers at different temperatures and different genetic constitutions, and from these values, *i.e.*, the instantaneous change in facet number instead of the direct facet counts, he calculates the coefficient of dominance according to Zeleny's formula. The following table contains the results for the heterozygotes between Full eye, Bar, and Ultrabar for reciprocal hybrids. The second line of headings designates the mothers of the heterozygotes (reciprocal crosses).

TABLE 12
(From Hersh)

T°	Full over Bar		Ultrabar over Full		Ultrabar over Bar	
	Bar	Full	Ultrabar	Full	Ultrabar	Bar
15	81.58	61.69	78.20	55.66	76.74	55.51
18	74.11	60.64	82.26	66.80	76.01	58.07
21.5	68.18	59.00	85.93	76.32	74.84	61.19
25.5	62.81	56.62	89.13	83.96	73.33	65.08
27.5	60.47	55.38	90.46	86.82	72.48	67.44
29.5	58.29	54.10	91.60	89.25	71.42	70.00

This shows that the degree of dominance in regard to the number of facets formed at a given moment changes regularly: it decreases in the $+/\text{Bar}$ case with increase of temperature from dominance of Wild type; it increases for dominance of Ultrabar

over Wild; it decreases or increases in reciprocal crosses for dominance of Ultrabar over Bar. Hersh draws the general conclusion from these facts that in its capacity as a modifier of growth during the course of development, the more dominant gene has relatively greater or less effect as the growth changes are affected by the temperature. He then seems to think that the activity or the potency of the two allelomorphic genes (which are thus complementary to each other) has been measured. I should prefer to assume that the temperature coefficients of the rates of the developmental processes controlling the beginning or end, etc. (see Fig. 23), of the facet forming (or facet-*Anlage* destroying) process have been measured or of such processes as control the underlying numerical system of cell divisions or of both. We shall again consider this same set of facts.

Hersh (1934*b*, *c*) returned later to the same problem in connection with the remarkable difference of temperature action upon Bar and Infrabar (Luce, see page 143). It will be shown in detail (page 143) that in experiments involving Bar, Infrabar, and the heterozygote, Bar is dominant at all temperatures. As Bar produces fewer facets with increasing temperature, but Infrabar more facets, the dominance of the heterozygote must increase in favor of Infrabar with a decrease of temperature. Near 17° this leads actually to a reversal of dominance, as illustrated in Fig. 29 (page 143). From this the conclusion may be drawn "that any theory of dominance . . . based on the quantitative serial order of the phenotypic effects at 25° would be inconsistent with a theory based on the serial order of the data at 17° or below." Such a conclusion does not, however, apply to the type of theory of dominance represented in Fig. 23; here only the difference of reactivity to temperature between Bar and Infrabar would have to be added as a further variable involved.

In the chapter on phenocopies, we mentioned that Friesen (1936) succeeded in producing the same types of phenocopies in *Drosophila* by the action of X rays as Goldschmidt (1929*a*, 1935*a*) had done by temperature shocks. Both shocks are supposed to act upon rates of reactions connected with morphogenesis. As we do not doubt that the shift of dominance is primarily also concerned with rates of developmental processes, we might expect that X rays will also be able to perform a shift in dominance.

Temperature shocks, finally, have also been found to influence dominance even in cases of complete dominance, where ordinary temperature effects are powerless. The heterozygous ebony flies (*Drosophila*) will show a certain amount of the recessive melanism if the larvae have been treated with temperature shocks (36 to 37°); in heterozygous vestigial flies, the same treatment might produce erect scutellar bristles which is one of the recessive traits of the vestigial fly (Goldschmidt, 1935*b*).

B. DOMINIGENES

For a long time it has been known that dominance may be affected by the presence of other genes acting as modifiers for dominance (*conditioned dominance*.) These genes might have a visible mutant effect besides this modifying action, and they might also be without any other visible effect. When it is impossible to separate such genes, they are sometimes spoken of as the *general genic environment* (Tchetverikoff). As a short term for such modifying genes, Goldschmidt (1935*b*) has proposed the word *dominigenes*. Bridges (1913) found that colored eyes in *Drosophila* were incompletely dominant to white in the simultaneous presence of the genes vermilion and pink. Lancefield (1918*a*) found in *Drosophila* a third-chromosome gene (semiforked) which shifts the dominance of Wild over forked toward the forked side. Landauer (1933) found a dominigene for the frizzle character of fowl, and Dunn and Landauer (1934) showed that dominigenes exist that shift the type of the heterozygote for Rumpless (a dominant mutation) toward the normal type. Lebedeff (1932) found for *D. virilis* that the recessive gene ruffled acted as a dominant in the presence of another gene rounded. Crew and Lamy (1932) found a similar case for *D. obscura*: the gene purple acts as a dominigene upon the heterozygote +/vermilion, vermilion being recessive. These last-named authors—the author believes the only ones—try to give for this action an interpretation, to which however we are unable to agree. They believe that genes in other loci may have exactly the same action as the pair of genes studied. Their presence might therefore interfere with dominance by an act of *quasi allelomorphism*. As in such a case three Nonwild-type genes would be present in the heterozygotes, the effect might become visible in the form of what looks like change of dominance

(Crew-Lamy, 1932). Another case in rodents is described by Burrows (1934). An unknown number of dominant dominigenes makes the heterozygote of Agouti and black intermediate instead of Agouti.

Such cases, according to Schultz (1935), do not seem to be rare in *Drosophila*. He found in 37 combinations of a heterozygote of one eye-color mutant with another homozygous mutant five cases of conditioned dominance, as the phenomenon is sometimes called, without being able to establish a rule connecting this phenomenon with the process of pigmentation, which we described on page 33. A few similar facts have also been known for rodents where recessive albinism and spotting may become incompletely recessive in the presence of other genes (Wright, 1927; Cuénot, 1911), and Snell (1931) described a case that he classifies as a change of dominance in an individual, in which at first dilution appeared dominant, whereas later the normal recessiveness was restored. The case is, however, not completely clear. Kikkawa (1934) described for *Drosophila virilis* an enhancing action of the gene confluent upon the dominance of plexus. But here another wing-venation gene is involved, and therefore the case might also be regarded from a different angle.

In some other cases, dominigenes were found after crossing: Harland (1932, 1934) found that a recessive mutation of cotton behaved as an incomplete recessive if crossed with different varieties which are supposed to possess dominigenes for this character.

A comparable case had been known for *Drosophila*. Morgan and Sturtevant (1929) found that in hybrids of *D. melanogaster* and *simulans* the genes Bar and Lobe are no longer dominant. Furthermore, the expression of Delta from *melanogaster* is less extreme, but the expression of Delta from *D. simulans* is more extreme in the hybrid than in the pure species.

A parallel case in mammals has been described by Green (1936) for the short-tailed mice, the genetics of which we mentioned before. He backcrossed heterozygotes of this dominant mutant to a normal strain; the resulting heterozygotes showed less dominance of the abnormality. The same heterozygotes were outcrossed to a different species (*bactrianus*), and still more normal tails resulted. In the first case, the introduction of one, in the second of more than one, dominigene is assumed. To the same class of phenomena belongs also Fisher's (1935) recent

work. He tested (from the standpoint of his phylogenetic theory, see page 121) the dominance of the dominant mutations in fowl. He found that after repeated backcrossing to the wild jungle fowl such genes were not dominant any more, probably because by this time some dominigenes, necessary for dominance, had been removed.

In some cases, the existence of dominigenes was proved by selection. Timofeeff (1925, 1934) selected for modifiers of two recessive abnormalities of the venation in *Drosophila funebris* and succeeded in establishing lines with incomplete recessiveness. A similar result was obtained by Stanley (1935) for the recessive vestigial wing. Finally, some cases ought to be mentioned that are more complicated because chromosome abnormalities are involved. Mohr (1929a) showed that the effect of the dominant deficiency Gull in *Drosophila* is lessened by the presence of the gene dachsous. Of course, a deficiency cannot strictly be compared with a heterozygote; this point will be discussed in another chapter. A similar observation is to be made, when it is reported that the addition of a duplicated fragment of a Wild-type chromosome in *Drosophila* to the recessive line does not result in a completely wild type (Dobzhansky and Sturtevant, 1932). Many possibilities are given to explain such cases within our general model. A very different point of view, the so-called *position effect*, will be discussed later in connection with the same facts.

The most thorough analysis has been made thus far by Goldschmidt (1935-1937) for the recessive character vestigial wings in *Drosophila*. Normal wings are completely dominant over vestigial. It was possible to isolate three dominigenes which shift the dominance toward the *vg*-type if all three are present. These are one sex-linked recessive allele of the cut gene and two autosomal dominants in the second and third chromosomes. If only the autosomal dominants are present in the *vg*/+ heterozygote, a small dominance effect is produced; *i.e.*, about 1.1 per cent of the individuals are nicked. The cut allele in homozygous condition affects similarly about 0.5 per cent individuals. If, however, all three dominigenes are present, all *vg*/+ heterozygotes are scalloped. The autosomal dominigenes in this case have an additive effect: for the degree of scalloping, namely nick to notched, (see page 57) increases from *AB/ab* to *AB/AB*. A gene was also

found that counteracts the effect of these dominigenes and is probably identical with the gene for black; in addition, the quantitative effect is different in both sexes.

In this case, further facts could be found which allow the drawing of conclusions upon the phenomenon of dominance (Goldschmidt and Hoener, 1937). In a former chapter, we reported (page 56) that the series of conditions of scalloping that connect the normal with the vestigial wing may be produced by a series

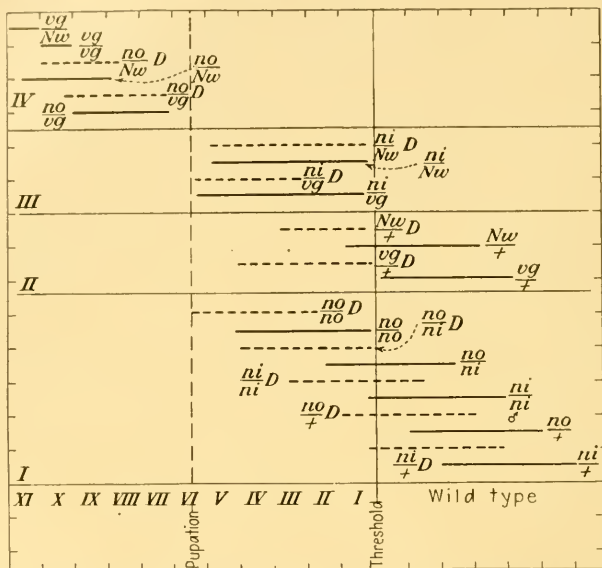


FIG. 24.—Graphic representation of the action of the dominigenes upon the phenotype of heterozygotes and homozygotes of the *vg* series. (From Goldschmidt-Hoener, 1937, *Univ. Cal. Publ. Zool.* **41**, Fig. 1.)

of multiple alleles of *vg* and the respective compounds. A similar series may be obtained by temperature action upon the *vg* homozygote (see page 12) and again by temperature or X-ray shock upon the Wild type in the phenocopic experiments (see page 8). It was further reported that the effect of these genes is the production of a degeneration of already formed wing tissue according to a definite pattern and that the degree of scalloping is proportional to the time of onset of the degenerative process (page 26). These facts have already been used to derive certain notions regarding the action of the gene, and we shall meet them again in the chapter on pattern (see page 229).

We may interpret them by means of a simple diagram (Fig. 24), based upon the following considerations. Different genic combinations produce different percentages of scalloped and normal, in orderly progression. As was pointed out before (page 67), this must mean that there is a threshold beyond which individuals are normal and a fluctuation that shifts part of the population across this threshold. This threshold line is found in the diagram as a definite time in development, beyond which the wing remains normal, and the fluctuation of each population is represented by the base line of the statistical curve of variability. To the left of the threshold follow the different degrees of scalloping from I = nicked to XI = no wing. The unbroken lines represent the range of fluctuation for populations of the different alleles and compounds (*cf.* Fig. 20, page 59). In the experiments to be reported, the dominigenes were added to all these genic combinations, and the broken lines represent these combinations. We see here that the phenotype of all the heterozygotes, homozygotes, and compounds up to homozygous notched are shifted in a perfectly parallel way toward less dominance of \pm normal, *i.e.*, to the left side of the diagram. This regular behavior in the action of the dominigenes is found up to class VI of scalloping but not beyond. Class VI is the maximum scalloping possible if degeneration sets in after pupation, and therefore the dominigenes in this case act only upon processes after pupation, *i.e.*, after evagination of the imaginal disks. The important point is now that the dominance-shifting action of the dominigenes works in a consistent quantitative way upon different heterozygotes as well as homozygotes of lower alleles: the shift is then not a shift of dominance but a shift in a process that is responsible for dominance as well as for the phenotype of the allelic series and their compounds (also for the phenocopic effect). Since it was stated earlier that these phenotypes are the product of different rates of one and the same reaction (*viz.*, the production of growth substances, or of lytic substances, see page 59), it follows that dominance also is a subphenomenon of the same system of reactions of different speed: dominigenes change this speed or one of the concomitant processes controlling threshold, etc. (see model Fig. 23), with the same quantitative effect upon the result as different alleles or temperature shocks produce. Only a system of the type of our model (Fig. 23) will

account for such a combination of consistently quantitative effects from different causes.

We shall return to this case in the chapter on dominance in allelomorphic series.

C. CHANGE OF DOMINANCE

In early Mendelian literature, occasionally changes of dominance within an individual were reported; *e.g.*, in the cross of red and yellow snails (*Helix*), the younger shells are yellow and become red later (Lang, 1908). Many similar cases have later found a different explanation or have not been studied sufficiently. But there are some cases known that actually may be described as a change of dominance. Goldschmidt (1917*d*, 1920*b*, 1924*b*) described such a case for the pattern of the caterpillars of *Lymantria dispar*. There is a race with bright-yellow epidermal markings which are visible through the transparent cuticula and remain constant through all instars. There is another race without these markings, except in very young stages, in which the cuticula is incrustated with dark pigment. In F_1 , the young caterpillars are light but, in the course of development, become darker and are finally all pigmented. This might be described as a change of dominance from light to dark. What actually happens is that the cuticular pigment in the hybrid is at first not present but slowly accumulates through the instars, thus covering the underlying bright markings. A comparison between the two races and the hybrid then shows that the gene for pigmentation of the dark race controls a rate of pigment production of such velocity that even the young caterpillar is deeply pigmented. The allele present in the light race controls a pigmentation process that is so slow that usually it does not produce visible pigment. The heterozygous gene (and also different alleles of the gene for pigmentation) controls a rate of pigment production that is intermediate; therefore the pigment covers the bright pattern only in later stages of development, which then explains the phenomenon of change of dominance in terms of rates of deposition of pigment.

Another case that lends itself to a similar explanation has been found by Honing (1923). He found a mutation of the Deli tobacco called *deformis* which among other characteristics has irregular narrow leaves endowed with excrescences on the lower

surface. The Deli, the deformis, and the hybrid plants begin development with normal leaves; deformis forms early the characteristic excrescences of the abnormal leaves. The hybrid begins a few weeks later with the same process, and the Deli race never does or does only later under certain conditions. This, again, looks like a change of dominance, but it is easily explained by the causation of chains of reactions of different velocities leading to the incidence of the abnormality and having three ascending velocities in the normal, the hybrid, and the abnormal race. Honing also derives this explanation as a parallel to the *Lymantria* case.

Later, Honing (1928) reported another instance. There are races of tobacco that need light for germination and races that do not. In young seeds of hybrids between such races, the need for light is dominant; in old seeds, recessive.

Another comparable case has been described by Ferwerda (1928) in the flour beetle (mealworm), *Tenebrio molitor*. Here a pair of allelomorphs control orange and brown color through all stages of life. In the hybrid, however, the larva and the pupa are more orange; the imago, brown. It is easy to derive an explanation on the basis of reaction velocities, considering the facts regarding melanin formation (discussed in other chapters). As a matter of fact, the case offers a close parallel to the development of larval pigments in *Lymantria*. Ferwerda derives such an explanation and constructs reaction curves for illustration. If the product of reaction is the amount of chromogen produced, the explanation derived for the pigmentation of *Lymantria* caterpillars also fits this case completely under the assumption that more chromogen is equivalent to deeper color. Other interpretations of the same general type are easily imagined.

D. DOMINANCE AND CHEMISTRY OF PRODUCTS OF GENE ACTION

A few facts of a chemical nature are available that may one day throw further light on the system of reactions within which the quantitative shift is supposed to account for the facts of dominance. We have already reported Schmalfuss' chemical models of the oxidation of chromogens. It was shown that a number of different factors influence the degree of this reaction, and it is conceivable that, as far as melanin formation is concerned, the model might be useful, showing that everything external,

internal, genetic, controlling these different conditions may act upon dominance. But no actual work on the chemistry of heterozygotes has been done.

There are also some data from Scott-Monerieff's work on anthocyanins which are relevant. Though this author is not inclined to lay down definite rules in regard to dominance, she points out some uniformity in behavior: plastid pigment, copigment, anthoxanthin, and anthocyanin are dominant to their absence. More oxidized and more methylated pigment is dominant over less oxidized or methylated. Diglycosidic and acylated anthocyanins are dominant over monoglycosidic and normal anthocyanin. More acid sap is dominant over less acid. It is obvious that such results may be interpreted in a general way in terms of reaction velocity, the phenomenon that we have always found in some way underlying the phenomena of dominance.

E. DOMINANCE IN MULTIPLE ALLELOMORPHIC SERIES

A considerable body of facts regarding dominance have been derived from the study of multiple allelomorphic series, and some of them have already been reported. A number of authors have realized that such facts may have an important bearing upon the understanding of gene action, *viz.*, Goldschmidt, 1917-1927; Zeleny, 1920; Wright, 1925; Hersh, 1930*a*; Dobzhansky, 1930; Muller, 1932*a*; and Goldschmidt, 1937. The pertinent facts up to 1930 have been brought together and analyzed critically in Stern's monograph (1930). We shall recount first the types of facts, closely following the grouping employed by Stern, as well as his examples, and then try to analyze them.

There is first the group of multiple alleles with a simple quantitative seriation of the effects, not considering now the cases of pleiotropic action of the same genes. Here the following types of behavior in regard to dominance are found:

1. Each higher allele is dominant over the lower one. Example: flower color of *Lathyrus*: *RR* self-colored dominant over *r'r'*; spotted, over *rr* white.

2. All alleles are intermediate in the compound. Example: the series of genes for eye-form Lobe in *Drosophila* +, *L*, *L*³, *L*²; the pigment series of *Lymantria* caterpillars.

3. The most frequently found cases show complete dominance of the highest member of the series over all others and intermediate behavior of all compounds not involving the highest member. To this group belong many of the best known series in animals and plants, *e.g.*, the white-eye series of *Drosophila* (wild, coral, blood, cherry, apricot, eosin, ivory, tinged, buff, ceru, white).

4. The theoretically most important is the case in which the situation is as in the last-mentioned group, but in addition the highest member is not dominant over the lowest ones. To this important group belong also the cases in which the lowest members are more or less lethal in homozygous condition. Examples of this type will be discussed in detail later.

5. Special cases requiring independent consideration, *e.g.*, the pattern of silkworm larvae: P^s striated, p^m dark brown, P normal, p unpigmented. From p^m to p the darker alleles are dominant over the lighter ones. P is dominant over the two lower alleles but only incompletely so over the highest p^m . But of course here no strict seriation is involved, as striped is a new character in the series.

There is a second set of facts which become visible when different effects of the same series upon different traits are involved (pleiotropy). Here the following possibilities are realized:

1. The different effects may be arranged in parallel series, and within these series dominance is also parallel, *e.g.*, the albino series of rabbits and mice affects in a parallel seriation black pigmentation, yellow pigmentation, and eye color; and in each the highest member is dominant, and the other compounds intermediate. But (as a threshold effect, see page 85) this does not mean that the highest member is always only the first one.

2. Within each series of pleiotropic effects, dominance behaves in an orderly way; but the series are not parallel in the different traits affected; *e.g.*, the aleuron-color and pericarp-color series in maize (R and P) affect the color of aleuron, vegetative parts, anthers, and pericarp. Everywhere deeper color is dominant over more dilute. But if the series of alleles is arranged for aleuron from dark to light, the effect upon the three other characters is not parallel; they have each their own seriations.

If, then, dominance is considered for all effects of one allele, it acts simultaneously as a dominant on one character and as a recessive upon another. An example from animals is the truncate series in *Drosophila* with consistent but not parallel actions upon wings and thoracic hair. In such cases, a special phenomenon may occur, if some of the alleles act only upon one of the traits. In the truncate series, the high allele T^{vo} does not affect the wings but the hair. The intermediate allele T^o affects the wings but not the hair. In the wing series, T^{vo} is dominant over T^o ; in the hair series, T^o is dominant over T^{vo} . The compound of both then produces a normal phenotype. There are finally the cases in which the action of multiple allelomorphs does not appear in a quantitative series, *e.g.*, the spineless and aristapedia alleles of *Drosophila*, the first affecting the bristles; the second, a homoeosis of the antenna. Here rather independent behavior of dominance in regard to the different traits occurs. A special type may be found if, as in the scute series of *Drosophila*, the alleles affect patterns of the same structure; each allele prevents the formation of definite bristles. In this case, the presence of the individual bristle in the pattern is always dominant over its absence, from which it follows that the compounds are always more like the Wild type than the effect of both ingredient genes would be. And if two alleles affect reciprocal parts of the bristle pattern, their compound must be Wild type. But such cases, though important in other respects, do not furnish special information for the problem of dominance.

We have now to find out whether such facts regarding dominance in multiple allelomorphic series furnish information on the meaning of dominance and therefore throw light upon the problem of the action of the gene. To do this we shall discuss first such cases as, according to facts already reported, permit one to draw definite conclusions. The best case in this respect is made out for the vestigial series. The dominance relations in this case are of the type as reported under 4 in the foregoing enumeration. Wild type is dominant over all alleles except the lowest member of the series, No-wing, which, in addition, is lethal in a homozygous condition. All the other compounds are intermediate and fit into their proper places between the homozygous alleles, as may be seen from Table 7 (page 80) and also from Fig. 24.

In this case, we have important information on some decisive points which makes possible a definite picture of the phenomenon.

1. There are first the facts concerning the lower members of the series. As reported above and discussed from different angles, these lower members produce their effects in a definite way. The lowest member nicked produces no visible effect in homozygous condition, according to Mohr. (In Goldschmidt's lines, there was a very small percentage of nicked individuals. The same shift as compared with Mohr's lines applies to other combinations which explains the small difference between the data in table 7, page 80, and those used for construction of Fig. 24. The difference is probably due to different modifiers.) The higher allele notched affects only 42.5 per cent individuals, and it is only with still higher alleles that 100 per cent effect is reached. If we represent these combinations and those compounds that range between them (see pages 110 and 111), as is done in Fig. 24, the effect of the allele is considered statistically as a curve of variation, a more or less large part of which is situated beyond the threshold for Wild type. (See also page 68, the first case of this type in *Lymantria*.) If we follow these curves from *no/no* with 100 per cent scalloping to *ni/ni* with only a few per cent scalloping, it is obvious that the curves for lower combinations, all within Wild type, ought to show a continuous shift to the right, as represented in Fig. 24. This is of course only an extrapolation; but it can be proved correct. In Fig. 24 are also represented as broken curves the actions of the same genes and compounds, with the addition of the dominigenes (see page 110). These shift the curves of the phenotypes to the left, and they do it, as the figure shows, in a way exactly parallel for the different combinations. Thus, the first heterozygote *ni/+* is shifted a little beyond the threshold, and all the higher compounds correspondingly more. This shows that there is actually within the Wild type a corresponding arrangement of more or less Wild-type individuals—degrees of Hyperwild, we might say, which thus far could not be distinguished phenotypically. To this series would also belong at their proper place the normal *vg/+* heterozygote (to be put between *ni/ni* and *no/+*) and the dominigene action upon it, which in Fig. 24 have been put into another group for certain reasons.

2. As just mentioned, there is a similar phenomenon at the other end of the series: No-wing/+ is not of Wild type but shows a certain percentage of scalloped individuals (1.3 per cent in Mohr's case, more in Goldschmidt-Hoener's counts). As Fig. 24 shows, this is shifted by the dominigenes to 100 per cent. In the usual language, this means that the extreme allele No-wing is somewhat dominant. If viewed in connection with the foregoing facts, it has a very different meaning, as it fits now into an orderly series. We know already (see page 28) that the scalloping effect is produced by destruction of already existing wing area, presumably by insufficiency of some growth substance or by accumulation of some lytic stuff. Let us now assume, adapting a deliberation of Mohr (1932) to the new body of facts, that the amount of growth substance—to use only this possibility; it could be just as well presented for lysis—produced by the alleles could be measured and that the threshold for the production of Wild type would be 40. (This method of analysis goes back to Goldschmidt's treatment of the allelomorphic sex genes in *Lymantria* since 1911; it has been used since, besides in work with sex-genes, by Wright (1925) for the series of coat colors in guinea pigs; by Stern (1929*b*), for the bobbed-series; by Ogura (1932), for the molting genes of the silkworm; and by Mohr (1932), for the *vg*-series.) The different types of scalloping would then be produced by values below 40, *i.e.*, insufficiencies, and these values may be read from a diagram like Fig. 20. Using an arbitrary basis, Mohr makes the following evaluation: No-wing = 6, vestigial = 10, notched = 15, nicked = 22, Wild = 30 for one gene. From this the compounds and heterozygotes may be calculated and are, according to Mohr:

$$\begin{array}{cccccccccccccccccccc}
 \frac{vg^{Nw}}{vg^{Nw}} & \frac{vg}{vg^{Nw}} & \frac{vg}{vg} & \frac{vg^{no}}{vg^{Nw}} & \frac{vg^{no}}{vg} & \frac{vg^{ni}}{vg^{Nw}} & \frac{vg^{no}}{vg^{no}} & \frac{vg^{ni}}{vg} & + & \frac{vg^{ni}}{vg^{Nw}} & + & \frac{vg^{ni}}{vg^{no}} & + & + & + \\
 12 & 16 & 20 & 21 & 25 & 28 & 30 & 32 & 36 & 37 & 40 & 44 & 45 & 52 & 60 \\
 & & & & & & & & & & & \underbrace{\hspace{1.5cm}} & & & \\
 & & & & & & & & & & & \text{Wild type} & & &
 \end{array}$$

This corresponds, of course, to the diagrams Fig. 20, 24 and shows the same orderly behavior and the series of different Wild types beyond the threshold of 40. Now, if we apply this enumeration to the problem of dominance in the series, we see that the combined action of a heterozygote or a compound

is always an addition of the actions of the individual genes or, in other words, always intermediate. The fact that Wild type is completely dominant in certain combinations shows that the Wild-type gene has in homozygous condition an action far beyond the necessary threshold (see Fig. 20); furthermore, that one Wild-type gene is not dominant but acts only as a dominant if the partner in the heterozygote has an action of such a quantity that $\frac{A+a}{2}$ reaches the threshold. If, however, this partner, as in the No-wing/+ heterozygote has itself such a low quantity of action that the quantity of the heterozygote falls below the threshold, Wild type is no longer dominant, and the lower member of the series is called a *partial dominant*.

Just as the correctness of these conclusions for the right end of the series could be proved by the parallel shifting action of the dominigenes, so it can be proved also near the threshold point by the action of the dominigenes upon the No-wing/+ heterozygote, which is shifted into 100 per cent scalloping.

3. The analysis of dominance in this case can be pushed one step further. In Fig. 20 (page 59), we presented the interpretation of the *vg*-allelomorphs in terms of reaction velocities, based upon the fact that with increase of the effect (destruction of wing area) the onset of the process of destruction occurs earlier and earlier in development. If we follow here only the interpretation for insufficiency of a growth substance, which might easily be translated into the one for lysis, the topmost curve in this figure represents the production of the growth substance just above the threshold for Wild type. Comparing this figure with Mohr's table on page 118, this curve would correspond to the value 40 of the table. The curve for Wild type would be far above this figure in the direction of the arrow, marked *hyper-wild*. As we know that the curve for heterozygous No-wing is similar to the nicked curve in the diagram, and as we have to assume that, *ceteris paribus*, the curve of the heterozygote is exactly between those of the homozygotes, the Wild-type curve would have to be drawn as far above the *ni*-curve as the *Nw*-curve is situated below it. Thus we realize that in this case dominance is based upon a system of developmental reactions, as described in our model (Fig. 23); the heterozygous gene produces an intermediate reaction which leads to a phenotypically intermediate

condition, whenever the threshold for Wild type is not transgressed. This threshold, however, is determined independently by other reactions, another variable. In the present case, the facts of development show that the threshold is identical with the time in development at which the differentiation of the wing *Anlage* in the pupa is finally determined. If up to this moment, which is controlled independently from the *vg*-gene, the growth substance has been available in minimum quantity, the normal Wild-type wing will appear. It is finally evident that dominigenes or environmental conditions may shift one or the other of these two known variables—as well as unknown others—with the effect of changed dominance conditions. It is also evident that it will be most difficult to accomplish such a shifting effect if the Wild-type gene is involved in the heterozygote. The reason is that the curve of this gene is so far above the threshold that only in the heterozygote with the lowest, almost lethal member of the series some individuals will remain below the threshold.

This best studied example (next to the Bar case in *Drosophila*, which belongs to another chapter, see page 143) then shows dominance as a function of the interplay of gene-controlled reactions and thus furnishes further evidence toward an understanding of gene action.

We have mentioned the different types of behavior in regard to dominance found in series of multiple allelomorphs. The question arises whether all these types may be interpreted on the same basis as the type case of vestigial. Let us consider first the cases in which each member of a series is dominant over the lower one. It is obvious that such a case cannot be explained with intermediate reactions and one threshold value for Wild type. We must rather expect some type of threshold conditions at each level. Such may easily be produced if the final reaction is not of a plus-minus type with all grades in between but of a strictly alternative type. Let us assume that a case of pigmentation is involved, as in certain actual cases (see Stern, 1930). We remember from the work of Scott-Moncrieff that usually the higher oxydized or methylated types are dominant. There is nothing intermediate between one or two methyl residues. If, then, two alleles differ by producing the final addition of one or two methyl residues to the pigment molecule, one must neces-

sarily be dominant. This model will account for all similar cases, whatever the details of the chemism may be.

There is no need for a special explanation of the cases of pleiotropy, in which each series of actions of the same gene has its own dominance relations. We have already pointed out (page 89) that the independent behavior of these different effects in regard to seriation is dependent upon the special developmental conditions of the different parts of the body. This means for the case of dominance that the variables of our model (Fig. 23) may be different for each organ involved with all the consequences for dominance, already reported. The same type of reasoning applies to those cases in which different alleles cause very different processes, *e.g.*, spineless aristapedia. But here another additional problem is involved, *viz.*, the problem of pattern, to which we shall return in another chapter.

F. THE PHYLOGENETIC THEORY OF DOMINANCE

Phylogenetic deliberations have nothing to do directly with the physiology of gene action. But, in connection with dominance, they may at least be mentioned, because the phylogenetic argument has silently assumed that dominance is a phenomenon of such a physiological type as had been developed in Goldschmidt's interpretation of dominance (1927*c*). As a matter of fact, Wright (1934*d*) clearly stated that this is the case and worked out his theoretical formulation of the physiology of dominance (see page 102) with the intention of furnishing a basis for a phylogenetic theory.

Fisher (1928-1932) has developed the theory that the dominance of Wild type over mutations is the result of a selection of modifiers which tend to shift the phenotype of the heterozygote toward resemblance to Wild type. He assumes that recessive mutations must have occurred always in sufficient number and therefore that heterozygotes were always present. If those heterozygotes which most resembled Wild type had a selective advantage, this would work finally to a selection of complete dominance by selection of genes modifying this dominance.

Wright (1929) and Haldane (1930) have published objections to this theory which, after all, it will be difficult to prove or disprove. But, as stated above, such a theory depends com-

pletely upon a knowledge of the physiology of dominance. The former discussions make it clear that the facts that physiological genetics have brought to light regarding dominance furnish a basis for such views as Fisher holds. But the decisive problem for the phylogenetic side is, of course, not the underlying developmental mechanism but the question of selection pressure, as discussed in the papers of Fisher's opponents, but which do not belong here.

Regarding the developmental system and its meaning for a possible selection process, some additional views have been derived, which are actually based upon the physiological facts.

Muller (1932*d*) realized that a theory of the phylogenetic evolution of dominance of the Wild type by selection of modifiers requires a physiological interpretation of dominance of the same type as the one developed by Goldschmidt (1927*c*) and proposes to look at the selection problem from a different angle. He postulates that the mutations of modifiers favoring dominance have been selected not so much for their specific protection against heterozygosis at the locus in question as to provide a margin of stability and security, to insure the organism against weakening genetic or environmental variability. "These modifiers must so affect the reaction set in motion by the primary gene in question as to cause this gene, when in two doses, to be near an upper limit of its curve of effectiveness, that is in a nearly horizontal part of the curve, not so readily subject to variation by influences in general, including reduction in the dosage of the primary gene." This, of course, presupposes an explanation of dominance of the type of our model (Fig. 23) and of the type proved to exist in the vestigial case (Fig. 20). The phylogenetic speculations (and calculations) on the selection of dominance modifiers then fall in line with the results derived from physiological genetics.

Simultaneously with Muller, Plunkett (1932) derived the same conclusion and expresses it in the same terms as those derived above from the vestigial case. He points out that Wild type is much less susceptible to environmental and other effects than the mutants. This, he says, is due to differences in the distance of the developmental process from its asymptote at the time when it ends; processes controlled by Wild-type genes usually closely approach their asymptotes, while those modified by mutant

genes may be terminated by the effects of other developmental processes while still very incomplete. Wright (1934) also comes to the same conclusions.

But another point derived from physiological genetics has also entered this discussion. In the vestigial case, we (Mohr and the author) found that it must be assumed that within the Wild phenotype many different degrees of Wildness must exist, all appearing alike on account of the threshold conditions, a view that had originally been derived in another field by Goldschmidt from the analysis of intersexuality for different grades of maleness or femaleness. In discussing Fisher's work, Haldane (1930) points out that selection might also have selected instead of modifiers, more potent Wild-type genes (what we called Hyperwild, far above the threshold). Muller (1932) set out to prove the existence of such Wild-type genes in different potencies. He used the findings of Timofeeff (1932) that a Russian race of *Drosophila* showed a different rate of mutation to white eye from the rate in the American race. Assuming that the Wild allelomorphs in this case may actually be different, Muller combined both of them with two white eye genes in a triploid condition (attached X's). He found that the American gene was less dominant than the Russian and attributes this to different potency, based on different levels above the threshold. We shall meet the same set of facts in a later chapter.

6. THE GENE IN DIFFERENT DOSES

The most elementary facts of genetics require the assumption that it is not irrelevant whether a gene is present in one or two doses. This quantitative view found its early expression in Bateson's *presence-absence theory* which claimed that a dominant gene is the presence, and the recessive the absence, of something. The heterozygote therefore contained one dose of a gene as compared with the two doses of the homozygous dominant. It is known that this theory has been disproved, at least in this its original form. Another type of quantitative view was introduced by Goldschmidt (1917) and claims that the quantity of the thing that is called a gene is important for the result of genic action and that gene and effect are linked, *ceteris paribus*, by the simple relation of a proportion between the quantity of the gene and the velocity of the chain of reactions controlled

by the gene. The (frequently misrepresented) derivation of this viewpoint was as follows. It was found that sex is determined by a balance between male and female sex determiners, one of them (the female ones in *Lymantria*) being constant for both sexes, the other (the male determiners in *Lymantria*) being carried by the X-chromosomes and therefore being present in either one or two quantities. These sex determiners in the X-chromosome behaved like single genes and were therefore considered as such. Then a series of genic conditions was found, which behaved genetically like a series of multiple allelomorphs of the sex gene and which shifted the balance in an orderly seriation from the value typical for 1 X through all intermediate values to the value characteristic for 2X (the series of intersexes). Since 1X or 2X, *i.e.*, one or two sex genes, obviously are two different quantities determining the value of the two balanced systems F/M and $F/M + M$, the series of intermediate values for the series of intersexes obtained in the experiments must represent different quantities of the sex genes between the quantity *one* (M) and the quantity *two* ($M + M$). It is certainly difficult to escape this conclusion, which is independent of the question whether M is one or a group of linked genes. It was strengthened by the proof that all the possible compounds of this series of multiple alleles had exactly the balance values that were expected from the known values of the individual members of the series (measurable by the degree of intersexuality, or sex reversal).

As it was simultaneously shown that these series of sex genes control reactions of definite velocities (see page 52) fit to be arranged in the same orderly way as the balance values, the conclusion was obvious that it is the quantity of those genes which controls the velocity of the reactions, *viz.*, the production of stuffs controlling sexual differentiation.

What was up to this point a logical inference from the facts soon was proved to be actually demonstrable. Standfuss (1907, 1908), who had produced intersexes in the saturnid moth by a species backcross (at that time not distinguished from gynandromorphs), realized the correct type of interpretation. After Federley's (1913) demonstration of triploidy in such backcrosses, he noticed that this abnormal number of chromosomes was responsible for the production of these intersexes. (Gold-

schmidt and Pariser, 1923, added the cytological facts later.) Much clearer was the demonstration in *Drosophila* by Bridges (1921b, 1922), where different quantities of autosomal and sex genes may be secured, among them the ratio 3A:2X producing intersexes. Here, then, the actual quantities of genes contained in visible numbers of chromosomes were shown to account for the abnormal development called intersexuality. Since that time, other similar cases have been found (for details, see Goldschmidt, 1931d). The generalizations derived from this analysis in regard to the nature of the gene and the multiple allelomorphs belong to a later theoretical chapter along with the discussion of some rather naïve criticisms. Here we are interested to know whether other facts exist that prove that the action of the gene is, *ceteris paribus*, proportional to its quantity; that an orderly series of quantities will lead to the typical effects seen in series of multiple allelomorphs; and that there is a relation between gene quantities and velocities of gene-controlled reactions of the type found in chemical reactions; and finally to learn whether facts exist to show generally that the quantity of a gene is one of its important properties.

A. DIFFERENCES OF DOSAGE PRODUCED BY THE 1X — 2X CONDITIONS

It is obvious that the mechanism of the sex chromosomes permits not only the study of sex genes in different quantities but also the study of all sex-linked genes in one or two doses. In the overwhelming majority of cases, one sex-linked gene in the heterozygous sex has the same effect as two in the homozygous sex or even a larger effect upon the phenotype. But there are also a few cases known in which the haplo-effect effect is weaker than the diplo-effect. Before discussing these facts and their meaning, we want to point out another set of facts that is pertinent to this problem.

1. Sex-controlled Phenotype.—There are numerous examples to show that one and the same genotype, except for the sex chromosomes, has a very different phenotypic expression in both sexes. We leave aside for the moment everything described as secondary sex characters and consider only cases of mutant genes outside the sex chromosomes, therefore present in both cases in duplex condition. There are innumerable cases in which such

homozygous mutant genes act alike in both sexes. But there are also numerous instances in which the effect differs in the two sexes. Some of these facts are of a type that might lead to an understanding of the phenomenon in terms of developmental physiology.

In *Lymantria dispar*, some of the geographic races are distinguished by different speed of development, different growth

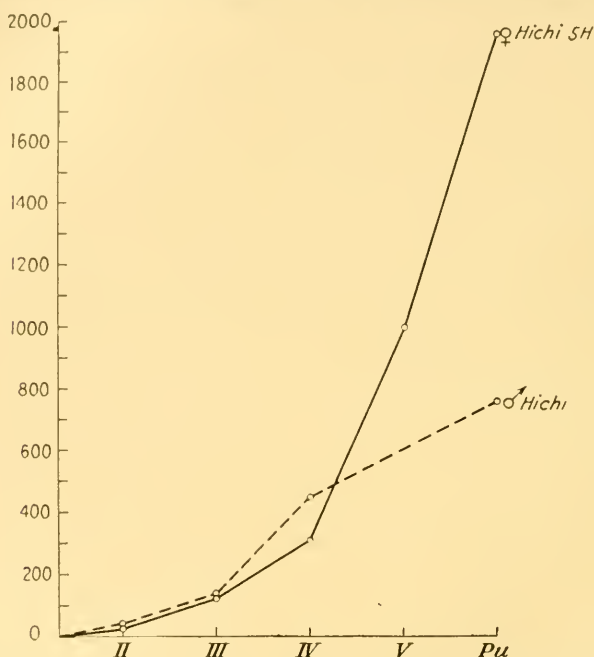


FIG. 25.—Growth curves of male *Lymantria dispar*, race Hichinoe, females with five moults, males with four. Larval instars plotted against weight in milligrams. (From Goldschmidt, 1933, *Arch. Entwicklmgemech.* **130**, Fig. 14.)

curves, different number of molts; and all these characters are typically different in both sexes (Goldschmidt, 1933a). But also the degree of difference between the sexes might be different in the respective races and might be controlled genetically. Figure 25 shows the growth curves for the two sexes of one of the races in which females have five and males four molts; and Fig. 18 gave similar curves for a number of races, showing the genetic differences. But, as is usually the case with growth, the difference is not one of single genes. In regard to the number of molts, how-

ever, the situation is relatively simple (see Goldschmidt, 1933a), as the different types are produced by a series of three multiple allelomorphs (parallel to the case of the silkworm, according to Ogura). T_1 homozygous produces four molts in both sexes; T_2 , four molts in the male and five in the female; and T_3 , five molts in both sexes. T_2 then has the same effect in the female as T_3 in the male; etc. It is further known from Ogura's work that in the silkworm occasionally a variation into the next lower or higher phenotype occurs, which we might have mentioned as a threshold phenomenon. It is further known that it is possible to shift the number of molts to a certain extent by the action of temperature (Ogura, etc., silkworm; Kuehn and collaborators, flour moth) or by hunger (Goldschmidt, *Lymantria*). These facts certainly reveal a genetic and developmental system involving a series of embryonic reactions of different velocities, capable of being shifted either by a mutant gene or by external conditions and exhibiting the phenomenon of threshold values. Within this system, the two sexes are found on different quantitative levels; i.e., a mutant gene or an external influence may raise or lower the curve of one sex to the level of the other in a different genotype. Such systems have been described repeatedly, and it has been shown that the resulting phenotype is a function of the genic action and all the other conditions of the developmental system. The autosomal genes involved in this case are identical for both sexes. What is different, then, is the developmental system. The X-XX mechanism creates two different developmental systems, probably in regard to the velocities of certain basic reactions, generally described in terms of metabolic rate. The reactions controlled by mutant genes, therefore, are facing a different situation in the two sexes. Let us assume for argument's sake that one of the differences, controlled by the X-chromosome mechanism, is the time at which differentiation ends. One and the same reaction caused by a mutant gene might then be ended at a different level in both sexes according to the different time limit for differentiation. If this reaction controls the incidence of a molt, it will occur or not occur according to the sexual difference just assumed. If the reaction consists in the oxidation of something, a higher or lower degree of oxidation will appear in one or the other sex. If this is true, it will follow that the appearance or nonappearance

of a sexual difference in regard to the action of autosomal genes depends upon the type of reaction involved and whether the quantity of its products, or threshold values for its action, are interfered with by the different conditions of the developmental system in both sexes.

A number of facts of the same general type as the previous example are available, all of which tend to corroborate the foregoing interpretation. There is a first set of facts not relating to specific genes but to general sexual differences. We have already mentioned the fact that it is possible to reproduce certain differential features of one sex as a phenocopy in the other sex by action of temperature shocks in the critical period. As a matter of fact, some of the earliest phenocopies produced by Standfuss, and also later by Federley and Kosminsky, in Lepidoptera were of this type (see page 4). A second series of facts relates to the action of temperature upon the phenotype of mutants. We reported earlier (see page 16) Driver's analysis of the Bar eye in *Drosophila* and Harnly's work on the vestigial wing. In both cases, the response was somewhat different in both sexes. In addition, it may be stated that the sensitive period for the action of temperature may be situated at different times of development. This is to be expected on the basis of such differences in the time relations of processes of differentiation as are known to obtain for the two sexes of many animals and which have been registered in all the work on details of growth. A third group of facts is of special interest because it contains a certain quantitative element. There are known mutational changes which are caused by the simultaneous action of a number of mutant genes with additive effects, and in some such instances these effects differ quantitatively in both sexes. According to Goldschmidt (1921b), melanism in the nun moth (*Lymantria monacha*) is caused by two autosomal and one sex-linked gene, which have an additive effect: if all three mutant genes are present in homozygous state, the wings are black; in their absence, they are white; and the different homozygous and heterozygous combinations produce all intermediate conditions according to definite rules. If we picture side by side a series of males and females of the same genetic constitution with increasing number of the three melanistic genes, we find the males always about one class of darkening ahead of the females; *i.e.*, a male *Aa*

looks like a female AA (the mutant genes are dominant); a male $AAbb$ like a female $AABb$; etc. This applies as well to the autosomal as to the sex-linked genes, since males with the sex-linked gene in heterozygous condition are much darker than females in simplex condition. Goldschmidt interpreted these facts by saying (1920, page 95): The cause must be sought in the physiological phenomena of pigmentation. Exact knowledge is lacking but the facts indicate that the genes for pigmentation control a definite increase in the quantity of pigment and that a given quantity covers the small wing of the male faster than the larger wing of the female. A better description would have to be given in the terms used above.

A similar example is also available from the work on the vestigial character of *Drosophila* (Goldschmidt, 1935-1937). Here, as described on page 109, a series of three mutant genes (dominigenes) shift the phenotype of the $vg/+$ heterozygote toward scalloped wings, and again the three genes, one of which is sex linked, have an additive effect. The effect, however, requires the presence of both dominant autosomal genes at least once in the female ($AaBb$), whereas males of the constitution $AAbb$ show the same effect. This case is of interest because many of the facts concerning development, phenocopies, and multiple alleles are known and furnish just such a system of developmental processes as is required for the explanation of the phenomenon with which we are concerned here.

A fourth group of facts which belong here are the facts concerning sex-controlled heredity. This term (Goldschmidt, 1920a) means that the phenotypic effect of mutant genes is suppressed in one sex, *i.e.*, is controlled by the specific features of sexual development. (It partly covers the older term sex limited.) Its actual basis can best be demonstrated in certain crosses of *L. dispar*. There are mutants existing in regard to the wing color of the male, not visible in the female. In a backcross or F_2 involving such mutants, the females are all alike; the males show the simple segregation as expected in all such cases of crossing with sex-controlled traits. If the cross, however, is such a one that the females become intersexual and assume male wing color, the segregation is also visible on the wings of the intersexual females (Goldschmidt, 1920c). A number of instances of sex-controlled heredity are known partly with very large phenotypic

differences, in which the underlying mutant genes have been analyzed, *viz.*, the case of *Papilio polytes* (De Meijere, 1910; Fryer, 1913), *P. dardanus* (Poulton, Ford, 1936), *Argynnis paphia* (Goldschmidt and Fischer, 1922), and *Colias edusa* (Gerould, 1911). Here mutant genes and their recombinations produce the phenotypes of the immensely different mimetic females, with normal Mendelian segregations, whereas the males are phenotypically constant but genetically identical with the females. In case of gynandromorphism (Goldschmidt and Fischer, 1927), the female parts may show one or the other sex-controlled type, whereas the male side is not influenced (see also Cockayne, 1935).

It is obvious that these facts also require for their explanation a developmental system, as described before in this chapter, a system in which the time relations of determinative processes in the development of one or the other sex are fixed in such a way that the action of the mutant genes reaches an effective threshold, or the production of the necessary amount of something, either in time for taking part in the following developmental processes or too late for this. In more detailed form, this idea is developed in Goldschmidt and Minami (1933) and Goldschmidt (1927c).

2. Dosage through Sex Chromosomes.—Now we may turn to the main subject of this chapter, the effect of different doses of one and the same gene, as produced in the two sexes in the case of sex-linked genes. As mentioned before, there is usually no difference of effect, and this may be for a number of reasons which are discussed below:

1. Sex-linked genes may be genes of such a high potency of action that the maximum effect that is physiologically possible is produced in the simplex condition. Haldane has pointed out that such a condition in the Wild type might have been brought about by selection in the past. But if mutant genes are involved, or even series of multiple allelomorphs, such an interpretation is not very probable.

2. Dissimilar effects of one and two genes in the respective sexes may be prevented by a system of dosage compensation, according to the idea of Muller (1932), who assumed that within the X-chromosome a number of modifying genes exist, which produce a compensating effect, which makes up for the lessened

efficiency of the gene in simplex condition. But there must be some reason for the existence of these dosage compensators, which cannot be expected to be present for eventual action upon mutations. Muller therefore assumes that they have also a similar action upon the Wild type, which thus is held high above its minimum threshold effect, and that consequently these modifiers have been evolved by selection after the manner of Fisher's theory (but independently of heterozygosis).

3. The interpretation introduced above to explain sex-controlled effects also explains the facts being considered here. This seems to me the most reasonable explanation. The sex-determining mechanism, acting through the control of the balance of the sex genes, determines not only the course of sexual development but simultaneously all the concomitant differences in metabolism and rate of differentiating processes. These differences are known to occur at the time when many mutant genes produce their phenotypic effect. For example, in many moths the males develop faster than the females, but pupal development takes longer in males (exact data in Goldschmidt, 1933a). Sex-linked genes will therefore produce the same effect in a simplex condition as in duplex, when the sex-controlled changes in the developmental system of the simplex sex run parallel to the change in gene action from duplex to simplex. If, for example, the reaction produced by one portion of a mutant gene reaches the threshold of action later than in the case of two portions, the effect of simplex and duplex will be the same, if the whole system of the simplex sex is such as to fit in with a later action of the respective gene. If this is not the case, the simplex gene will have a different effect—a lower one if the shift is in one, an even higher one if the shift is in the other, direction. This explanation which covers sex-linked genes both with or without rate effect, also with increased effect of simplex, and which fits this phenomenon into the whole system of action of genes, as revealed in physiological genetics, seems superior to the phylogenetic explanations of dosage compensation.

If this is the case, the difference or lack of difference in the effect of one or two doses of sex-linked genes furnishes no direct results for the problem of the action of genes in different quantities. The effect, whatever it is, is not produced under the conditions of *ceteris paribus* but in two different physiological systems.

The question remains whether or not some of the detailed data available point in the same direction. The most extensive set of facts known thus far relates to the eye-pigment series in *Drosophila* at the white locus of the X-chromosome. In Table 13, the phenotypes are arranged serially from dark to light for the female.

TABLE 13

Sym- bol	Name	♀	♂	Simplex compared with duplex
W^{eo}	coral	deep pink	still darker	increased
W^{bl}	blood	pink	pink	equal
W^e	eosin	pink	pinkish yellow	decreased
W^{ch}	cherry	pinkish	darker	increased
W^a	apricot	pinkish yellow	darker	increased
W^i	ivory	pale yellow	lighter	decreased
W^t	tinged	very pale pinkish	very pale pinkish	equal
W^{bf}	buff	light brownish yellow	light brownish yellow	equal
W	white	white	white	equal

These data show the presence of all three possibilities of simplex effects in one series of alleles. It is remarkable that a chromosome rearrangement exists, the so-called pale translocation, which affects the eye colors of this series. Those that are lighter in the male are still lighter, and those that are darker are still darker. The pale translocation has therefore the same effect as the sexual difference of the system of development. Other eye-color modifying genes with comparable effect are known, *e.g.*, pinkish, which dilutes male more than female eosin (Stern, 1929a). These facts point to the same type of explanation as before: the effect of the modifiers certainly works through a set of reactions different from that controlled by the white series. Here a change in the interplay of different developmental reactions is patent. As the effect is of the same type as the sex effect, we might reasonably attribute it to the same causes. It must be agreed, though, that it will be difficult to devise a detailed form of such a system to cover also the irregularity of behavior within the series.

We have mentioned Ephrussi and Beadle's transplantations of *Drosophila* eyes, to which we shall return later. When sepia eye disks were implanted into vermilion hosts, a sex difference in pigment development appeared (1937), the males being lighter. Transplants performed with disks of different age showed that the surroundings cannot be made responsible for the effect, which must be caused by conditions in the disk itself. This does not contradict the former conclusions, as the disk is itself a developmental system in which the pigment-forming reactions are only a part of all reactions.

B. DIFFERENCES OF DOSAGE BY DEFICIENCIES

Next to the instances of sex-linked genes, mutant genes lying opposite deficiencies, *i.e.*, deletions of a part of the chromosome, provide the most illuminating material on the action of genes in single doses as compared with double doses and the heterozygote. Though deficiencies are known for many organisms used in genetic experimentation, most of the information pertaining to the present problem comes from work in *Drosophila*. Mohr (1923*a*) discovered that most mutant genes contained in a section of a chromosome opposite a deficiency in the sister chromosome had in this their simplex condition an exaggerated effect; *e.g.*, a light eye color was still lighter, a forked bristle extremely forked. This applies to the majority of mutant genes thus studied by Mohr and his followers, with the exception of mutant characters which seem to be already at the extremest, physiologically possible level, like white eyes, prune, purple, and yellow. A first explanation for this phenomenon was given by Bridges (1922), who assumed that the deleted piece of the chromosome contained a number of modifiers the removal of which upset the balance of the genes in favor of a more extreme action of the mutant gene. This interpretation was not very probable at the outset, as it ought to lead in different cases to results of opposite character, since it can hardly be supposed that the deleted pieces always contain only one type of modifiers. Mohr, moreover, could show that the phenomenon is independent of the length of the deletions in one region, which also rules out the balance interpretation. Goldschmidt (1927*c*) proposed a different explanation, based upon the general idea that the activity of the genes is proportional to their quantity. If, for example, the

mutant gene for eosin eyes produces a smaller quantity of pigment (or a lower grade of oxidation) than the wild-type allelomorph, the seriation of decreasing quantities produced will be $+/+ > +/w^e > w^e/w^e > w^e$; i.e., one w^e leads to less pigmentation than two w^e . As the condition produced by the homozygous recessive w^e/w^e is regarded as the mutant type, the effect of one w^e will be still further away from normal, i.e., exaggerated in comparison with the homozygous recessive. This interpretation, which in itself is independent of the assumption that the mutation from $+$ to w^e was a change in quantity (an assumption strongly suggested by these facts), has since been proved to be correct. The proofs, derived from the study of the effects of more than two recessives, will be discussed in the next chapter. They have been accepted as valid by Stern (1930), Mohr (1932), and Muller (1932). The last-named author has proposed to call mutations, which produce a lessened effect (slower rate of reaction according to Goldschmidt) and therefore show this dosage phenomenon, *hypomorphs* (which seems unnecessary) and has added a number of other instances, all of the same type. These facts, then, actually show that in this case the effect of a gene is proportional to its quantity.

In a considerable number of the cases studied, the facts reported above led to the conclusion that the action of the mutant genes consists in changing rates of reaction of the special physiological process involved in the production of the phenotype. The phenomena just reported then prove that, in these cases at least, the velocities of the respective reactions are, *ceteris paribus*, proportional to the quantities of what is called a gene. This proved fact might or might not justify the extension of this view to the primary differences between the Wild type and the mutant gene. The author's impression is that it is not at all easy to evade this conclusion, but the discussion of this point belongs to the chapter on the theory of the gene. It may be added, however, that the majority of gene mutations, according to Muller (1932), are of this hypomorphic type.

Muller (1932) refers to a number of cases which, though they show that the dosage of a gene has a typical proportional effect upon the end product, yet differ in important points from the simple relations just reported. He points to Mohr's work on the behavior of abnormal abdomen in different doses. The

difference from the cases just reported is that the homozygous mutant gene has a more extreme effect than one dose plus deficiency. The seriation here is from the standpoint of maximum abnormality: $Ab/Ab > Ab > Ab/+ > +$. He calls such mutants, which apparently do not act in the same direction as the Wild-type allele but in a different direction altogether, though to a lesser degree, *antimorphs*. Leaving aside the question of whether or not the cases ranged in this group belong actually to gene mutations, it must be pointed out that the difference between the two cases is not a difference of the type of mutation but a difference concerning the processes controlled by the genes in question, a difference in physiology of development. In the case of the eye pigment, the mutant gene produces less pigment or less oxidized pigment; it is deficient in action, or, more correctly, it controls a lower velocity of reaction; one dose therefore must have the minimum pigment-producing effect. In the case of the abnormal abdomen, the effect of the mutant gene is to produce a situation that prevents normal segmentation or normal concrescence of the segments, whatever the immediate cause may be. Inspecting the different degrees of this effect, we realize that the gradation of the effect is proportional to the time of onset of the disturbing feature. The mutant genes then control a reaction that leads to a threshold of action at a definite time of development. Two doses of the gene will, just as in the pigment case, produce a faster reaction than one dose. In this case, however, faster reaction means earlier onset of the disturbance and therefore more extreme disturbance. This deliberation shows that the cases that Muller calls antimorphs lead to exactly the same conclusions in regard to the effects of gene dosage as the others, if viewed from the standpoint of genic action in development. Further material bearing upon these problems will be found in the next chapter.

C. DIFFERENCES OF DOSAGE BY ADDITION OF GENES

The elaborate knowledge of *Drosophila* genetics has made it possible to build up individuals that contain series of different dosages of one gene and thus to test further the influence of gene quantity upon the product of genic action. One such case has been available for a long time, though it was realized only recently—the case of the Bar-eye mutants, which will be discussed shortly.

The first systematic attempt to attack the problem of the relation of gene quantity to gene action by gene addition was made by Stern (1929*b*) with the bobbed allelomorphs. The Y-chromosome of *Drosophila* contains the mutant gene bobbed, the normal allele of which is situated in the X-chromosome. As hardly any other genes are situated in the Y-chromosome, and as this has very little effect upon development, the number of *bb*-genes could be varied by adding more Y-chromosomes or Y-chromosome

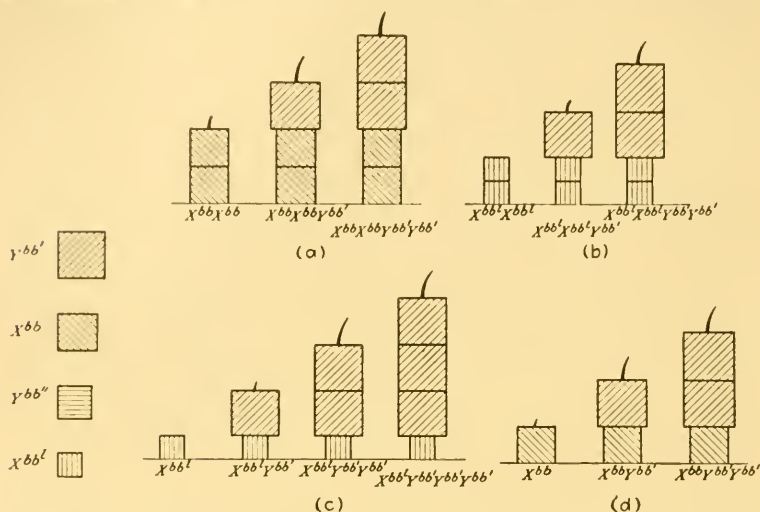


FIG. 26.—The squares on the left side: The relative quantities of the four *bb*-alleles *bb'*, *bb*, *bb''*, and *bb^l* as derived from the length of bristles. X and Y indicate the position of the alleles. The diagrams a-d: action of different combinations of *bb*-alleles. Each combination shows the respective bristle. *ab*, female; *cd*, male combinations. (From Stern, 1929, *Biol. Centrbl.* 49.)

fragments. In this way, males could be composed with from zero to three bobbed genes, and females with from zero to two such genes. Bobbed produces short bristles. In these combinations, the length of the bristles is directly proportional to the number of the *bb*-genes, up to the Wild-type length, which acts as a threshold condition, beyond which no increase seems possible, at least in this series. [As a modification by temperature action, bristles of twice the length of Wild type may be produced (Goldschmidt, 1935*a*)]. One might also express the result by stating that the increase of numbers of recessive genes leads toward and finally to the dominant Wild phenotype. The experimental series and its result are represented graphically

in Fig. 26. These are incidentally the facts to which we alluded in the last chapter as proofs of Goldschmidt's interpretation of the exaggeration phenomenon.

A number of comparable facts have become known since. Muller, League, and Offermann (1931) produced series of gene quantities for such mutant genes of *Drosophila* as scute, cosin, apricot by adding small fragments of the chromosome in question containing the respective mutant locus, which had been secured by irradiation. For most of the loci the results parallel completely those of Stern and lead therefore to the same conclusions.

It is in these same experiments on dosage changes that Muller *et al.* found the less simple behavior, as reported earlier, for one-dose relations in the case of deficiencies, in which two doses of the mutant gene have more effect away from normal than one. The probable explanation was given on page 135 for Mohr's example of abnormal abdomen. Muller (1932) mentions another somewhat different case. Homozygous hairy wing is twice as hairy as heterozygous. Adding the normal allele in a duplication does not change the situation. On the other hand, a duplication containing the Hairy gene added to a normal individual makes it hairy. One might express this as dominance of Hairy wing over one or two doses of the normal allele (Muller calls this a neomorphic mutation. We are speaking here, with Muller, of genes and alleles, though probably all the cases thus far allotted to this group are major changes in chromosome architecture, like translocations). It is too early to consider these facts in simple terms of dosage, but there is another case, which Muller puts in the same category with his neomorphs and which is most thoroughly known and therefore more suitable for an analysis. This is the case of Bar eye in *Drosophila*.

Bar eye was originally described as a semidominant mutant reducing the number of facets in the eye. Subsequently, a number of what seemed to be mutations arose at the same locus, partly more, partly less, reducing the number of facets. The one that is important for our present discussion is Zeleny's Ultrabar, reducing the number of facets to about 25 under standard conditions (Normal 780, Bar 68). The next important step was Sturtevant's (1925) proof (see also L. V. Morgan, 1931) that Ultrabar is Double-Bar, two Bar "genes" being located in the same chromosome as a consequence of unequal crossing over

(L. V. Morgan). This discovery makes it possible to compare the Bar gene in four different quantities with Normal, without any other locus being involved. The effect of Bar is to reduce the number of facets and may therefore be expressed in facet counts. Table 16 is compiled from Sturtevant's data (B^+ = Wild, B = Bar, BB = Infrabar):

TABLE 14
(From Sturtevant)

Genotype	Number of facets at 25°	Number of B	Number of B^+
B^+/B^+	779.4	0	2
B^+/B	358.4	1	1
B/B	68.1	2	0
B^+/BB	45.4	2	1
B/BB	36.4	3	0
BB/BB	24.1	4	0

This and other work have led Sturtevant to conclude that no Wild-type allelomorph to B exists. The chromosome which was known to have lost the Bar-gene by unequal crossing over had no other influence upon Round eyes than the normal Wild-type chromosome. The series then would give the actual effect of one to four doses of B in terms of reduction or of production of facet number. The reducing effect obviously increases with dosage of the B gene. (The difference between B/B and BB has been explained as so-called *position effect*, see page 304.) In an analysis of these results, Goldschmidt (1927c) pointed out that the results might be interpreted on the basis of reaction velocities of a process responsible for facet formation. If we assume that it is the number of divisions of the primary retinula-forming cells that is decreased by the reaction controlled by the Bar gene, we may visualize this reaction as the production of a division promoting substance, which either reaches the necessary threshold too late and therefore acts for too short a period or is not produced in sufficient quantity to last long enough. We might also visualize the reaction as producing something that stops these divisions prematurely or as producing an insufficiency which destroys already formed cells (as in the *vg*-case). Embryological facts will have to decide between such possibilities (see the work of Margolis discussed on page 76). But in any case it is perfectly

clear that we are facing here a series of facts showing that a definite gene acts through controlling reaction velocities proportional to its quantity. We have discussed (see page 104) the manifold facts regarding this gene that enhance the safety of this conclusion. We shall add one significant fact: Hersh (1934c) calculated from Driver's data on temperature effect that the curve of reaction controlled by the Bar gene is a sigmoid curve, which would mean that the differences between the members of the series in regard to this reaction do not represent merely developmental arrests of the process at a greater or lesser distance from a common upper asymptote but that the termination of the process is approached asymptotically. This seems to point more to a process of the type realized in the *vg*-wing than to an influence upon cell divisions.

The Bar series has furnished additional important material upon the problem discussed here, which is derived from the fact that another mutation, Infrabar B^i , was found which may be combined with all the others and may also be obtained as double Infrabar by unequal crossing over. The facet counts of all these combinations are available, and many have been tested at different temperatures.

Infrabar, which in usual terminology is one of the multiple alleles of Bar (see, however, page 143), differs from the rest of the series in some properties. The eye facets are not only fewer than

TABLE 15
(From Sturtevant)

Genotype	Number of facets 25°	Number of B^i	Number of B^+
B^+/B^+	779.4	0	2
B^+/B^i	716.4	1	1
B^i/B^i	320.4	2	0
B^+/B^iB^i	200.2	2	1
B^i/B^iB^i	138 ±	3	0
B^iB^i/B^iB^i	38.2	4	0

in Round (Wild type) but also irregularly arranged. The strangest difference, however, is the reaction to temperature. Whereas in the Bar and Ultrabar alleles facet number decreases with rise of temperature, it increases in Infrabar (Luce, 1931). Special dominance features of Infrabar will soon be mentioned.

We shall consider first the effects of different quantities of Infrabar, which have been obtained in a parallel series to Bar, according to Sturtevant (1925) (Table 15).

We see a perfectly parallel series to the one recorded for Bar, again showing that the Infrabar allele also acts in different dosages proportional to its quantity.

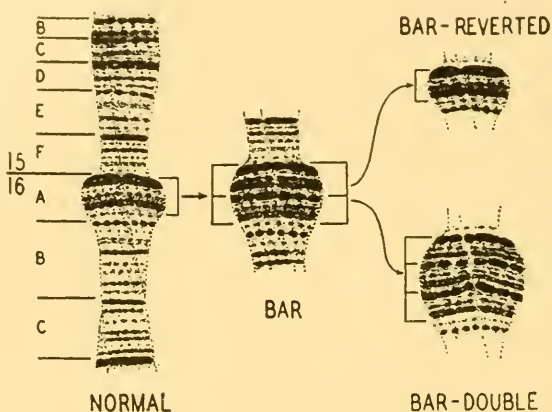


FIG. 27.—Salivary chromosomes of *Drosophila* at the Bar-locus. (From Bridges, 1936, *Science* 83.)

These two sets of facts in which the actually known different doses of the alleles and the normal allelomorphs fit into an orderly arrangement suggest that the Wild type, the Bar, and the Infrabar alleles are all different quantities of what was supposed to be a gene. The first two of these conclusions drawn by Goldschmidt (1927*c*) have now been proved correct. Bridges (1936) and also Muller *et al.* (1936) have shown that the Bar mutation is an internal duplication of a small section of the X-chromosome (Fig. 27). Two such sections then represent Bar, and three Ultrabar or Double bar. This new fact makes it possible to analyze the case further. A series of increasing combinations of B^+ and B represents, then, a series of two to six doses of this chromosome section. If we assume, for reasons

discussed above, that the action of these "alleles" consists in destroying facet-forming material during development (parallel to the destruction of wing material in the vestigial case), we may express the actual facet numbers as percentages of the number in the Wild type and represent the action of the genes as the percentage destruction of facets. This is done in the first group of Table 16, and Fig. 28 gives the curve obtained from these data (the crosses are values of this series). From the curve we may

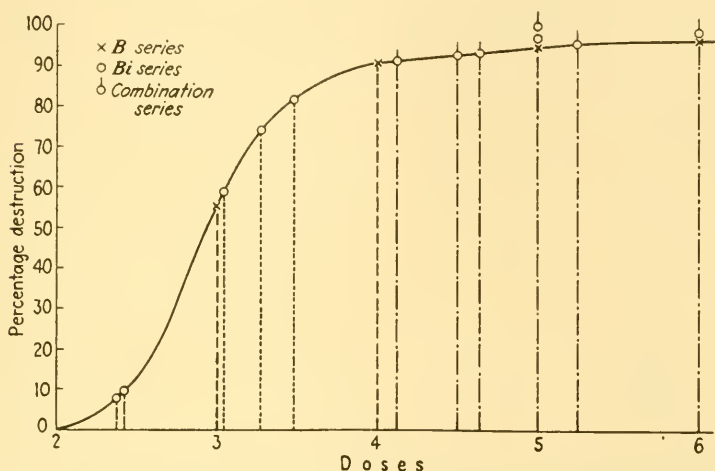


FIG. 28.—Curve plotted for the Bar and Infrabar series. Plotting actual and interpolated doses against percentage destruction of facets.

now calculate the eventual dosage of Infrabar. If this allele also represents a dosage difference from the Wild-chromosome section, it must be a dose between one and two. If we designate as X the difference between the Bar duplication ($2B^+$) and the Infrabar of smaller dosage (between 1 and $2B^+$), the Infrabar locus contains the dosage $2B^+ - X$, or one dose B^+ and one $B^+ - X$. The different combinations of B^+ and B^i contain then different doses of $B^+ - X$, as tabulated in the second section of the table (second and third columns). To prove that B^i is a dosage difference, viz., $2B^+ - X$, we mark the percentage loss of facets in the B^i combinations on the curve obtained for B (the points \circ in the seriation of the table). The corresponding points on the abscissa (dotted lines) tell us which dosage of $B^+ = 1$ would have been needed to produce this effect in the Bar series, which fur-

nished the curve. If Infrabar is actually a dosage difference like Bar, a calculation of X from all these points for the Infrabar series must give identical values. This has been done in the second section of the table (fifth and sixth columns), *e.g.*, for B^+/B^i $3 - 1X = 2.4$ $X = 0.6$; *i.e.*, Infrabar is a 40 per cent addition to the Wild locus.

TABLE 16

	Number B^+	Number add. $B^i =$ $B^+ - X$	Per cent facet loss	Value found in terms of B^+	X	Facet number
B^+/B^+	2	..	0			779
B^+/B	3	..	54			358
B/B	4	..	{ 91			68
B^+/BB	4	..	{ 94			45
B/BB	5	..	95			36
BB/BB	6	..	97			24
B^+/B^i	2	1	8	2.4	0.6	716
B^i/B^i	2	2	{ 59	3.0	0.5	320
B^+/B^iB^i	2	2	{ 74	3.3	0.4	200
B^i/B^iB^i	2	3	82	3.5	0.5	138
B^iB^i/B^iB^i	2	4	95	5	0.25	38
B/B^i	3	1	91	4.1	-0.1	73.5
B^+/BB^i	3	1	93	4.5	-0.5	50.5
B^i/BB	4	1	94	4.6	0.4	41.8
B/B^iB^i	3	2	95	5	0	38.3
B^i/BB^i	3	2	95	5	0	37.8
B/BB^i	4	1	95	5	0	37
B^iB^i/BB^i	3	3	96	5.3	0.2	27.9
B^iB^i/BB	4	2	97	6	0	26.7
BB^i/BB^i	4	2	97	6	0	26.7
BB/BB^i	5	1	97	6	0	24.1

The values are seen to vary between 40 and 75 per cent addition; B^i then would be about $1\frac{1}{2}$ Wild or $\frac{3}{4}$ Bar dosage. This calculation is made in a rough way without curve fitting, but the result looks positive.

The next consequence of this analysis would be that the combined dosages of B and B^i ought also to fit into the series, *i.e.*, give identical values for X . The same calculations have been made

for this group (the points \bigcirc in the curve and the third section of the table). A glance at the column for X shows that this is not the case. X is mostly zero or even negative. This may mean one of two things: Either B^i is not a dosage difference from B^+ like B (in this case, the consistent results of the second section could not be accounted for); or there is an additional disturbing feature in the third section of combinations which has to be analyzed.

We have already discussed the dominance relation of the Bar series in another chapter, the special features of which had

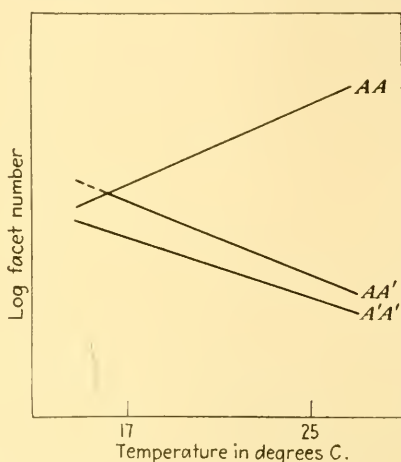


FIG. 29.—Semilogarithmic plot of the relation of facet number (*Drosophila melanogaster*) to temperature in two sets of homozygous females and the corresponding heterozygotes. AA, Infrabar; A'A', Bar; AA', Barinfrabar. (From Hersh, 1934, *Amer. Naturalist* 68.)

already induced Zeleny, Goldschmidt, *et al.* to special discussions. Wright (1929) called attention to the fact that in the combinations of Bar and Infrabar, with which we are here concerned, Bar behaves as an almost complete dominant, keeping Infrabar from expression. This is, of course, another description of the non-quantitative results of the third section of Table 16 and of the value 0 for X in terms of dominance. But this description is true only for Sturtevant's experiments at 25°. Luce (1931) showed, as already mentioned, that Infrabar has a different temperature relation (thermophene) from Bar, the number of facets increasing instead of decreasing with temperature. The

heterozygote, however, follows closely the Bar thermophene, the Bar gene thus being dominant for the whole facet-temperature relation. Figure 29 gives the curves constructed by Hersh (1934) for these relations. It shows as one of the consequences of the divergence of the temperature-facet curves for B^i , B , and B/B^i that at lower temperatures the heterozygotes assume more and more the B^i type and finally, just below 17° , reach it, so that here B^i appears dominant over B . The additional fact regarding B^i action is then its different thermophene, which leads automatically to dominance of Bar at higher temperatures and makes a simple quantitative arrangement of the data impossible, when B and B^i are simultaneously present. (Hersh, 1934, however, points out that a single order for all temperatures is obtained if not the end result—the number of facets—is used as a measure, but the instantaneous increase in facets at all temperatures measured by the algebraic value of the first derivative, see page 105).

The old discussion, whether the whole Bar series is quantitative or qualitative, thus resolves itself into the following: the Bar components are all quantitative, and the series of Infrabar is also quantitative. But Infrabar has, in addition, a different quality, which is expressed in its different thermophene and therefore makes the phenotype not simply dependent upon the quantities involved, when Bar and Infrabar are both present. We know that B is a double dose of a small but differentiated chromosome segment. What Infrabar is, is not yet known. If it is, as the genetic data indicate, a duplication of only a part of this region, the lack of the rest of the region would have to account for the different qualities. At present, the analysis may not be pushed further. There remains, of course, the question whether or not one may draw a conclusion from this case concerning the action of the gene, since usually such a duplication would not be called a gene mutation. This question will be answered later when discussing the theory of the gene.

The Bar series has always served as a typical example for a series of multiple allelomorphs and has therefore been cited too by Goldschmidt when he tried to prove that such series are based upon different quantities of the same gene. The proof of actual dosage (with the necessary additions for B^i) in this case requires a comparison with other cases in which both actual dosages and

allelomorphic series have been studied. The case that started such deliberations has already been discussed, *viz.*, the sex races of *Lymantria*, where the actual dosages 1 and 2 are known and the series of alleles fits in between in an orderly way. A similar case has been worked out by Stern (1928, 1930) in connection with the different quantities of the Bobbed gene in *Drosophila*, the effects of which were reported on page 136. In this case, a number of alleles of the Bobbed gene (*bb*) in the X- and Y-chromosome were found, called, in Stern's terminology, X^{bb} , $Y^{bb'}$, X^{bbl} , $X^{bb''}$. All of these have a different effect upon bristle length. From the different combinations that may be built up Stern estimated the relative activity of these alleles and found the series

$$\begin{aligned} + &= 30 \\ Y^{bb'} &= 10 \\ X^{bb} &= 8 \\ Y^{bb''} &= 4 \\ X^{bbl} &= 2 \end{aligned}$$

It is now possible to make series of combinations of these alleles together with dosage differences, as reported above. The result is that dosages and alleles fit together perfectly in their respective effects in all combinations studied. Figure 30 represents these results as a curve, in which the ordinate indicates length of bristle (III normal, I very short); the abscissa gives the different combinations of alleles and dosages arranged according to the values calculated for them from the preceding figures. The curve coincides with the assumption that the alleles represent dosage differences.

In discussing these facts, it has to be kept in mind, however, that multiple alleles may be of a very different type; a translocation with visible effect at the same locus as a known mutation acts as an allele, though both actions may have a completely different base. The same applies to deficiencies. But this again leads to the problem of the theory of the gene.

The questions put at the beginning of this chapter (page 125), then, may be answered thus:

1. Facts are known that prove that the gene (or chromosome segment) may act, *ceteris paribus*, proportionally to its quantity.

2. Such series or orderly actions are of the same type as the visible effects of the majority of multiple allelomorphs.

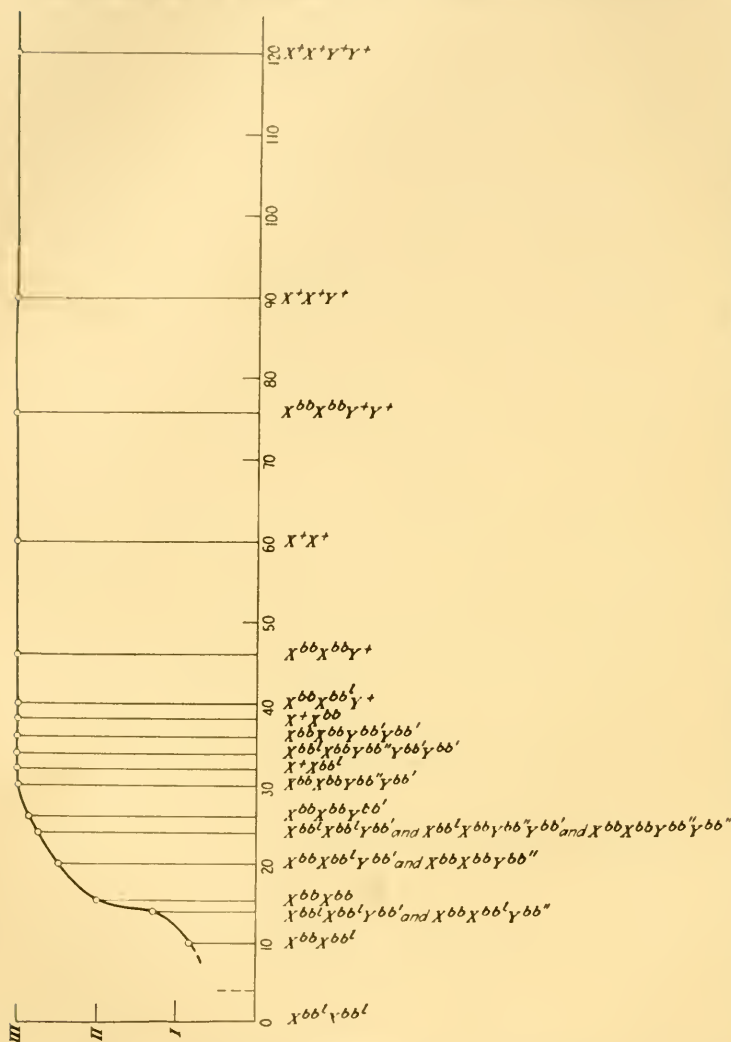


FIG. 30.—Effect of the bb -alleles in diploid *Drosophila* females. Ordinate: bristle length. I, short; II, intermediate; III, normal. Abscissa: the different combinations of genes arranged according to the sum of their individual effects based on the assumption that the effect of $X^{+} = Y^{+} = 30$; $Y^{bb'} = 10$; $X^{bb'} = 8$; $Y^{bb''} = 4$; $X^{bb''} = Z$. (From Stern, 1930. *Handb. Vererbwiss.* 14.)

3. A relation exists between gene quantities and velocities of reaction.

4. The typical nature of such cases shows that the quantity or dosage of a gene must be considered as one of its important properties.

D. DIFFERENCES OF DOSAGE NOT CONFINED TO INDIVIDUAL GENES

Differences of dosage may also be produced by chromosomal rearrangements, which add (or subtract) parts of a chromosome or whole chromosomes to the chromosome set, as already stated. In an ascending order, such dosage alterations would be:

1. Loss of a whole chromosome if viable. Example: haplo-IV in *Drosophila*.

2. Loss of a considerable section of a chromosome. Example: large deletions in *Drosophila*.

3. Loss of a small section of a chromosome. Example: the typical deficiencies.

4. Addition of a small duplicated fragment. Example: the Bar case.

5. Addition of a larger duplicated fragment. Example: many duplications in *Drosophila*.

6. Addition of an extra chromosome. Example: all the manifold trisomies in plants.

7. Additions of more than one extra chromosome up to a whole set, *i.e.*, subtriploids to triploids. For the dosage of one gene the groups 4 to 7 mean always triplicates; groups 1 to 3, simplex condition.

8. Addition of more than one single whole chromosome, tetrasomies, etc.

9. Addition of more than one whole chromosome set, tetraploidy, etc.

10. All combinations of these types are imaginable.

It is clear that in all these cases no direct conclusions upon the action of the gene may be drawn, because differences in the dosage of many genes are always involved. Nevertheless, in a general way, we are dealing with the same phenomenon of dosage increase that furnishes information upon the action of groups of genes in different dosage. From the standpoint of developmental physiology there is only a quantitative difference between these types of a dosage effect. There can be no doubt, in the light of the cases reported above, that any deviation from the typical dosage of a gene, resulting in different reaction velocities, disturbs the normal setup of the interplay of the different simultaneous and consecutive determining reactions. The result is an abnor-

mal development within the sphere of influence of these reactions. The more genes are involved in such dosage differences the larger this sphere of influence will be, and the more general the effect. This conclusion, of course, is a direct consequence of the idea that genes act together by controlling rates of reactions in development, which have to be in proper tune in order to produce the typical effect. The working of such a system to control development was first conceived in a more generalized way (not related to gene action) by Guyer (1911). It was later derived from actual experiments in change of gene dosage on the basis of Goldschmidt's discovery and analysis of the phenomenon for which he coined the term *intersexuality* (1912, 1915) and was later elaborated as a general principle of physiological genetics (1920*b*). Bridges (1922) coined the term *genic balance*, which is frequently used to describe these facts, though he did not think of minutely interwoven reaction velocities but of an effect of different genes pulling the phenotype in a plus or minus direction. This seems too crude a way of describing the case. In using the term genic balance, it must certainly be kept in mind that the balance, or, in Goldschmidt's terminology, the quantitative relation or the tune, is not one of the genes but of the gene-controlled reactions.

In this way, the dosage relations mentioned above are supposed to lead to a considerable upset of the balance of the gene-controlled reactions concerned with development. It is in this sense that facts of that type will lead to insight into the physiology of genic action. It is not possible to recount all the phenotypic effects caused by those compound changes in dosage. But there are a number of facts that might furnish some information toward our problems.

There is first one set of facts in which the action of individual genes is studied but where the quantitative steps have been produced by addition of whole chromosomes or chromosome sets. Here are a few examples to which ought to be added innumerable cases in which the same mutant gene has been compared in haploids, diploids, and tetraploids.

Mangelsdorf and Fraps (1931) studied the vitamin content of corn, which is higher in yellow than in white corn. As the endosperm is known to be triploid, it is possible to build up kernels containing the recessive genes for white in 0,1,2,3 doses in the formulae (Y = yellow, y = white) yyy , yyY , yYY , YYY .

The phenotype of these classes is white, pale yellow, dilute yellow, deep yellow. An assay of the vitamin A content of these four genotypes actually showed its quantity directly proportional to the number of *Y*-genes, *viz.*:

TABLE 17

Number of <i>Y</i> -genes	Vitamin A Units per Gram
0	0.05
1	2.25
2	5.00
3	7.50

Each *Y*-gene, then, produces about 2.5 units of vitamin.

Similar examples may also be taken from other endosperm work. Thus, Lindstrom and Gerhardt (1927) found a cumulative effect of the number of starchy genes in maize. As a matter of fact, such relations were already indicated in the first work done on endosperm characters by Correns (1899). A special study was recently made by Rhoades (1936). The case is somewhat complicated in detail. The main feature is that dotted aleurone occurs on corn kernels when a gene *Dt* is present together with the gene *a* for colourless aleurone and three more primary genes. The decisive point is that kernels on the same ear may be compared which are identical in all the other genes but contain 1,2,3 *a*-genes. The result in regard to the number of spots was a simple linear progression with the number of *a*₁-genes (different numbers of the *Dt*-gene were, however, not additive). Another example is Nawashin's (1930) work on allotriploid hybrids of *Crepis tectorum* and *C. alpina*. The former species has short achenes; the latter, long ones. In the allotriploids, as compared with the parents and *F*₁, a definite seriation of the length of the achenes is found, strictly proportional to the number of alpina (*a*) and tectorum (*t*) chromosomes, *viz.*,

$$2t < 2t + 1a < t + a < 1t + 2a < 2a.$$

Gowen (1933*a*) found additive effects similar to those reported in corn when comparing the effects of the Hairy gene in *Drosophila* in diploids and triploids. Bridges (1922) and Schultz (1935) worked on the fourth chromosome of *Drosophila*. The latter used the fourth-chromosome character shaven which shortens and removes bristles. He compared the effects in different dosages in diploids and triploids, and the results are proportional

to the quantity considering the diploidy or triploidy of the other chromosomes, as Table 15 shows:

TABLE 18
(From Schultz)

	Haplo IV <i>sv</i>	Diplo IV <i>sv</i> / +	Triplo IV <i>sv</i> / <i>sv</i> / <i>sv</i>	Tetra IV <i>sv</i> / <i>sv</i> / <i>sv</i> / <i>sv</i>
2N	Extreme <i>sv</i>	Type <i>sv</i>	+	Extra bristles
3N	Dies	Extreme <i>sv</i>	Slight <i>sv</i>	Slight <i>sv</i>

Dosage differences of this type will be found in many cases of polyploidy and hyperploidy, and examples may be cited from innumerable cases in plants, in which individual genes are compared in different dosages within these systems and produce quantitatively increasing effects. Some important facts derived from the study of tetraploids by Lawrence and Scott-Moncrieff will be reported in a later chapter.

At this juncture, it ought to be pointed out that in all cases where multiple factors show a simple additive behavior a simple quantitative relation may be involved. If we take, for example, Nilsson-Ehles' classic case of the color of oats, the quantitative effect of one to six multiple genes may be based upon each gene's contributing something to the amount of oxidase produced (or chromogen or time of onset, etc.). In most cases, a further analysis is not possible. Where, however, the individual genes have been isolated, as in the nun-moth case, (see page 128) and their individual action is known, conclusions upon the action of different quantities of similar genes may be drawn. There are, of course, many pitfalls to be reckoned with. To mention only one: Rasmusson (1933) finds that multiple genes do not act in an additive way but more in the form of an interaction with a combined effect lower than required if additive. Such a result may mean very different things in terms of gene action, such as a threshold or saturation effect, as in the bobbed case of Stern; a mutual dependency of different reactions leading to the same end product; saturation effects only within individual members of the series; disturbance of time relations; disturbance of reactions by others. In any case, conclusions must be carefully weighed.

There follow now the cases in which one chromosome may be obtained in simplex, duplex, and triplex condition, without regard to individual mutant genes. Such is the case, for example, for the fourth chromosome of *Drosophila* (Bridges). As this is small and supposed to contain few genes, the effects ought to be of a comparatively good dosage type. A haplo-IV fly is distinguished from a normal one by smaller body size; shorter and more slender bristles; paler body color; darker thoracic pattern; larger and rougher eyes; slightly spread, blunt, and cloudy wings. A triplo-IV fly, containing three fourth-chromosomes, shows small and smooth eyes; narrow, more pointed wings; darker body color; suppressed trident pattern. In other words, the three dosage types 1,2,3 fourth-chromosomes form an orderly series of quantitative expression of a number of phenotypic traits in the order subnormal-normal-hypernormal expression. It may be added here that the presence of the mutant gene *eyeless* in this chromosome leads to a comparable dosage effect for this gene alone.

Other examples of the same type may be found in Blakeslee's (since 1921) work on *Datura*. The interpretation in terms of velocities of gene-controlled reactions is the same as given above for the action of individual genes. The difference is that there only one or a few interwoven reactions were changed in their time relations, and correspondingly some special somatic traits were shifted proportionally to dosage and affected reaction velocity. In the case of whole chromosomes, which are probably concerned with many, and therefore decisive, reactions, general developmental features are affected, and therefore abnormalities of practically the whole animal will result. In plants, the phenotypic expression of such a dosage change will appear predominantly as a change of the whole habitus which becomes visible at once and which might be described in quantitative terms for each discernible character. It is important to mention the fact, first discovered by Blakeslee in *Datura* and later found in other plants, that the phenotypic effect of a triplex condition of one chromosome is typical and different for each chromosome, showing that the genes affecting general developmental processes like size, type of branching, and growth type are not distributed at random among the chromosomes.

The genic-balance-theory, in the form used by Bridges, expresses these effects as follows. The plus and minus modifiers, the balance of which determines for each character its condition in the Wild type, are distributed at random along the chromosomes. If one chromosome is removed, it will usually happen that more plus than minus modifiers (or vice versa) for one or for several characters will be removed. Consequently, more of the other type will be left in action, and the character will be shifted in that direction. Apparently, not much meaning can be attached to this form of description as far as the action of genes in controlling developmental processes is concerned. It seems advisable, therefore, to discard the term genic balance in favor of balance of gene-controlled reaction velocities.

A special problem of dosage effect is presented when whole chromosome sets are involved in polyploidy, and therefore the dosage of all genes is increased concomitantly. What may be changed in this case is (1) the proper relation of gene action (if proportional to dosage) to the cytoplasmic substratum. (2) The threshold for the maximum effect of gene doses may be different for different genes; therefore at a higher dosage some may increase their effect proportionally, others not (when their threshold is reached). This, again, would result in a disharmony in the time of the reactions. The effects of polyploidy might therefore also be used to a certain extent in analyzing genic action. It is generally known that polyploids might be more or less different from the diploids. Muentzing (1936) has recently reviewed all the known cases and compiled an extensive table showing the effects of abnormal number of chromosomes in natural chromosome races of plants. He states that hardly any cases are known in which no differential features from the normal diploid could be found. He then compares the natural polyploids with the experimental ones and comes to the conclusion that the effects are the same. It is generally known that these effects are mostly quantitative in regard to all parts of the plant, producing the gigas type, though the details may vary in different cases. It is generally assumed that these differences are the result of the increase in cell size as a consequence of the existence of the karyoplasmic ratio, making cell size proportional to chromosome number. But there are also exceptions due to the fact that there is an optimum beyond which chromosome number may not

increase without impairing the vigor of the plant. The position of this optimum differs in different cases. It would be difficult to draw direct conclusions upon genic action from such facts.

There are, in addition, numerous physiological effects of polyploidy, which, in part at least, may be directly caused by the change in cell size. But it is questionable whether all effects may be caused in such a way. From the long list of facts that Muentzing has compiled from botanical literature it follows that most quantitative traits are influenced; *e.g.*, the growth curve and the time of flowering are retarded. According to Wettstein and his students, this is a consequence of a change in rate of cell divisions. In other cases, the osmotic conditions are changed; the starch or vitamin content is increased; resistance to cold is heightened; general metabolism and chemical composition are changed. The few cases in animals (*Artemia salina*, according to Artom, 1920, 1926; Gross, 1932; psychid moths, Seiler, 1927) seem to show parallel traits. Most of the authors agree that all these effects are in the end caused by the change of cell size. If this is the case, the physiological facts do not lead further than the morphological ones, in so far as our problem is concerned.

But there is a more indirect way in which the study of polyploids has contributed to the knowledge of the action of the gene. In his extensive experiments on polyploidy in mosses, Wettstein (1924*b*) found that in pure races the experimentally produced polyploids show a simple geometric increase of cell volume with chromosome number up to the possible limit of about $4n$. This limit, in regard to addition of more chromosome sets, may, however, be shifted considerably if hybrids are used for the experiments. In this case, up to 16 chromosome sets could be attained. This is possible because in such hybrids the increase in cell size is regulated so that the additional growth is no longer proportional to the chromosome number but decreases with further addition of genomes. This regulation of cell size occurs according to a definite curve (Fig. 31) which reaches its maximum asymptotically. The equation of this curve is identical with the equation of a monomolecular reaction. Wettstein had formerly shown that genes exist in the pure species that control the basic cell volume as well as the proportionality factor for its geometrical increase with chromosome number and that these genes differ in both species involved (*Funaria*, *Physcomitrella*). He assumes,

therefore, that in the hybrid these two genes work against each other and thus control the asymptotic increase in cell volume. As the curve of the combined effect is the curve of a monomolecular reaction, he concludes that the action of the genes in this case is of this general type and follows the mass law

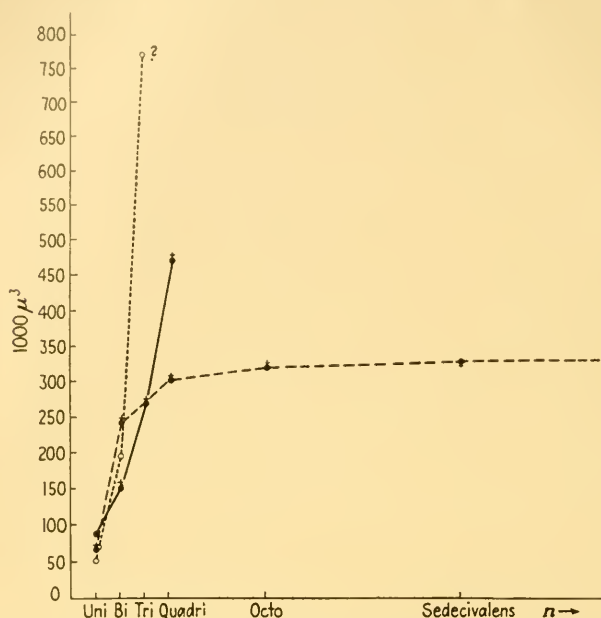


FIG. 31.—Curves for cell volume in polyloid mosses (n to $16n$ chromosomes) and — pure species, --- hybrids with regulation. (From Wettstein, 1924, *Biol. Zentralbl.* 44.)

of reaction. This conclusion then coincides with those derived from many other facts.

E. THE HETEROZYGOTE AS DOSAGE DIFFERENCE

In a former chapter, the facts relating to the gene in heterozygous condition were analyzed. We mentioned there the presence-absence theory and also the possibility that a pair of genes differ quantitatively. In cases of multiple alleles, it could be said at least that the activity or potency of a pair of alleles was different in quantity, whether this meant quantity of the genes themselves or not. It was then found that in cases of actual quantities, as in the Bar case, the heterozygotes fitted into the seriation. All this suggests that mutant differences are

frequently dosage differences between the two alleles. Facts are therefore of interest that show that the action of the heterozygote shows simple quantitative relations to that of the homozygote. Many such cases have already been mentioned in the chapters on rate genes and on multiple allelomorphs. One, in which the type of reaction has been analyzed, might be added here, *viz.*, the pigmentation in the Himalaya rabbit. Here only the "akra" of the body (tips of ear, nose, paws, tail) are pigmented according to a multiple allelomorphic series of colors. W. Schultz (1915) proved that after plucking hair on the white parts of the body, pigmented hair of the expected color is regenerated, if the temperature is decreased below 11°C. Iljin (1926) found this temperature different for the different akra, and it may be modified by experimental changes of skin temperature (Schultz, 1929; Iljin, 1932) produced by cutting the sympathicus or by hyperthyroidism. Even different races with different critical temperature were found. Engelsmeier (1935) showed that these differences are based upon differences in skin temperature and that the critical skin temperature above which no pigment is formed is constant though dependent upon the genotype, *e.g.*, a^n/a^n , 33.2°C.; a^n/a , 30.6°C. This would mean that the Himalayan gene produces a pigment-forming reaction with a phenotypic alternative according to the skin temperature. As the akra are normally the coldest points, this type of mosaic pattern is the result of the alternative reaction norm together with the outside conditions (cooling of akra).

Schultz (1928) succeeded also in producing the blackening effect in explants of skin. In this case, it is not the temperature at the time of pigment formation that is decisive but the temperature at the time of exposure before actual pigment formation. It might therefore be assumed (Engelsmeier) that the oxidase is formed only at low temperature and that its amount is dependent upon the time of cooling as well as—with time constant—upon the genes present (one or two quantities). Actually, with the formula a^n/a^n , 5 min. in 25° sufficed for pigment formation in explantations of white skin, whereas a^n/a individuals needed 10 to 20 min. cooling. These experiments demonstrate as well the alternative norm of reaction as its quantitative side as correlated with the quantity of a process (probably enzyme production) and its dependence upon the gene quantities. There

is an additional difference in the reactivity of back and belly skin.

It is difficult to decide whether or not we may actually speak here of dosage differences. This is, indeed, permitted only if the normal allele is ruled out. Ordinarily, this would not be permissible. But it is quite possible that in some cases the effect of one $+$ -gene upon a certain character is below the threshold and therefore equal to zero in terms of phenotypic effect. The presence of one or two doses of the mutant gene would in such cases actually amount to a dosage difference. It will be difficult to decide when such a situation may be assumed. A criterion may be found in the actual proof of different rates of reaction in the heterozygote and mutant homozygote.

7. THE INTERACTION OF THE GENES

One of the first facts that were realized in the first decades of Mendelian work was that the phenotypic expression of an individual mutant gene depends upon the condition of all the other genes that might influence the character. A mutation in one of these other genes will collaborate in controlling the phenotype. This insight, which was derived partly from the earliest classic work on plants, partly from that on rodents, found a different expression in general terms. It formed the basis of such representations of genic effects as the ones used first in Goldschmidt's textbook (1911), *viz.*, dichotomic determination tables. It was expressed in the earlier textbooks of genetics (Johannsen, Baur, Goldschmidt) by saying that in describing the effect of the pair Aa , tacitly $BBCCDD$, etc., ought to be added. The later development of genetics has not changed this general position though a different terminology became established. The sum total of other genes influencing the phenotype is frequently called the *internal genetic environment* (Tschetverikow); or if a main mutant gene may be discerned controlling a definite character, the others, which all together form this genetic environment, are called modifiers. Thus, of course, each mutant gene may act as a modifier for any other, though such actions will not always become visible. But the more thoroughly the effects of individual mutant genes become known the more the influence of the other genes becomes visible and may be expressed generally in terms of modifiers, if these modifying genes cannot be described

by a visible action of their own. Many examples of this type have been mentioned in the preceding pages. We have discussed also the development of these genetic formulations into formulations in terms of genic action, the theory of the balance or proper tune of gene-controlled reactions.

In this field, there is a considerable body of special facts which may be significant in connection with the problems of this book. Certainly not all cases of genic interaction can be discussed, as this would amount to a review of all the details of special genetics. Only certain facts will therefore be mentioned that throw direct light upon the problem of genic action or that have been found in connection with studies devoted to this problem.

As mentioned before, the colors of the hair of rodents represent one of the characters that has been used for a study of genic interaction since early Mendelian days. A considerable number of facts have already been reported in other chapters (see page 88). Referring to these, we may now consider the additional data that apply to the problem of genic interaction. Wright has emphasized this side of the problem, and his analysis (1927) is the most complete one.

Wright's studies on rodent colors have been mentioned in connection with the problems of multiple allelism (page 87) and also in regard to the chemism of genic action (page 91). In the same work, also, the interaction of different genes controlling the skin color was studied. The main factors influencing pigment belong to a black (*sepia*) series and to a yellow series. There is, in addition, the albino series of allelomorphs, which has been discussed; a dilution series; and others that control the pattern of pigmentation. Altogether seven series of allelomorphic factors and many of their combinations are known. The combinations of the albino series with *sepia* and yellow, respectively, have already been reported (page 88), and Wright's interpretation has been given (Wright, 1925). These same series were combined with a dilutor, the pink eye factor *p*, the brown factor *b*, and the dilution factor *f*; and the color grades were measured with the color wheel. Among these effects the first to be considered is the difference between the yellow and the black series which is caused probably by the production of two melanins. This production is, however, not completely independent. Factors like *b* and *p* may act on yellow or *sepia*

production alone. The genes *e* and *a* decide between the production of one or the other. Others like *c* and *s* may act upon both through an antecedent process. The albino series determines differences in quantity of pigment irrespective of quality and is therefore put in the last group. It has been mentioned that the order of effects is not the same if the albino series is combined with sepia or with yellow, and, moreover, the seriation of effects is not identical for colors of eyes and hair. In Wright's own words:

Factor *C* is a condition for the most intense colors of both series (red and black), factors *C^k* and *C^d* determine very nearly the same grade of dilute yellow but widely different intensities of sepia. With factors *C^r* and *C^a* no yellow whatever develops but with *C^r* there is an even more intense sepia than with *C^d* in the fur (less intense in the eyes) while with *C^a* there is no visible sepia at birth though a small amount develops later in the skin and fur under the influence of cold.

Table 19 contains a partial summary of these data in terms of color-grade evaluations, only the homozygotes (no heterozygotes and compounds) being considered.

The explanation that has been proposed was that the albino series produces a graded series of effects on a single process essential to all pigmentation; furthermore, that the irregularities of the different series are explained by the assumption of a different threshold of effectiveness of the immediate products in the case of yellow or sepia; since each of these is determined independently, each individual gene behaves in this respect as an independent unit. These thresholds may also be different regionally (eye and fur). In addition, the assumption is made that there is a competition between the yellow and black processes in the black forming parts of the fur. The gene *b* modifies the pigmentation of the sepia series in such a way as not to affect the thresholds of sepia and yellow or the competition between them. *P*, however, has a different effect in regard to the order in the series, from which it is concluded that it raises the threshold of sepia from a point close to the gene level of *A^a* nearly to *C^r* (besides weakening the pigment-producing powers—dilution—of the substance involved). The factor *f* reduces the intensity of yellow and causes complete absence of the kind of sepia determined by *p*. Both effects are supposed to occur inde-

pendently of those already mentioned. These results may be summarized in graphic representation in Fig. 32 (from Wright). The average grades of sepia (solid), brown (dot and dash), and yellow (dash) are given in the combinations of the albino series

TABLE 19
(From Wright)

Average grades of sepia and brown in different combinations

<i>C</i> series	<i>FPB</i> sepia	<i>FPbb</i> brown	<i>FppB</i> pale sepia	<i>Fppbb</i> pale brown	<i>ffPB</i> sepia	<i>ffPbb</i> brown
<i>C</i>	21	15.63	9.7	8.29	20.91	16.0
<i>C^kC^k</i>	20.10	14.61	9.08	7.22	19.0	
<i>C^dC^d</i>	16.88	14.18	4.88	5.43	16.79	15.0
<i>C^rC^r</i>	20.09	15.47	2.58	2.82		
<i>C^aC^a</i>	0	0	0	0	0	0

Average grades of yellow in different combinations

<i>C</i> series	<i>FF</i> yellow	<i>Ff</i> yellow	<i>ff</i> yellow
<i>C</i>	10.57	9.92	6.77
<i>C^kC^k</i>	7.10	1.20
<i>C^dC^d</i>	6.97	6.46	1.60
<i>C^rC^r</i>	0	0	0
<i>C^aC^a</i>	0	0	0

Average grades of pale sepia or of yellow

<i>C</i> series	<i>FFppBB</i> pale sepia	<i>FfppBB</i> pale yellow sepia	<i>ffppBB</i> cream
<i>C</i>	9.70	7.60	2.15
<i>C^dC^d</i>	4.88	3.40	0
<i>C^rC^r</i>	2.58	0	0

and the *f*, *b*, *p* gene mutations. *E* means black; *e*, yellow parts of the fur. This analysis of genic interaction, which thus far is the most elaborate one, again shows the genes at work in the way expressed before as a system of reaction velocities in tune.

As a kind of supplement to this analysis it might be mentioned that Hadjidimitroff (1933) found that the amount of pigment

deposited in a rabbit's hair is constant for a given genotype. Therefore, the phenotypic expression is correlated to the length of the hair, longer hair showing more diluted color.

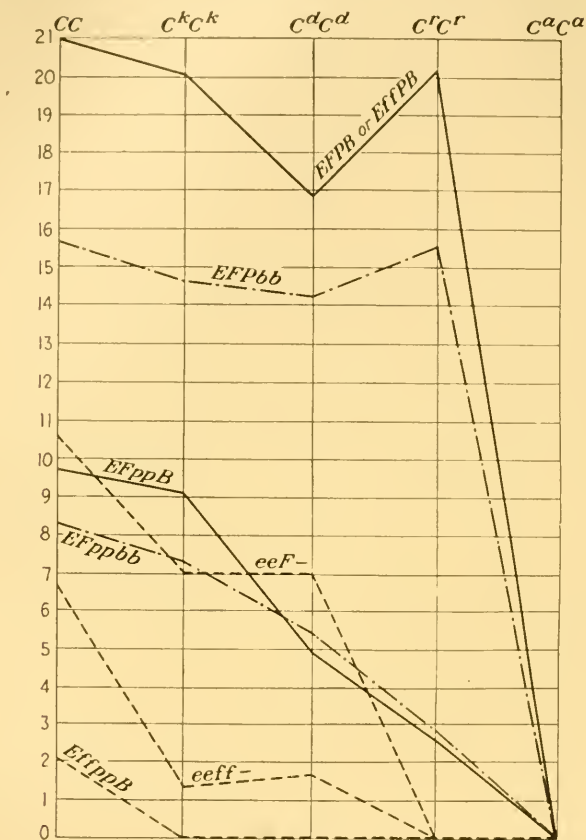


FIG. 32.—Action of color factors in the guinea pig. The average grades of sepia (solid) brown (dot and dash) yellow (dash) found with particular combinations of factors of the series F_1 , P , and B with the five homozygotes of the albino series. Factor E is used to indicate reference to black parts of the fur, and e to yellow parts of the fur. (From Wright, 1927, *Genet.* **12**, Fig. 8.)

In connection with this work, another type of genic interaction which has been studied in rodents may be mentioned, and the related facts might also find their place in the chapter on dominance. One Mendelian character in rodents upon which much work has been done since the first studies by Cuénot is Spotting in its different aspects. Spotting is usually caused by a major

gene which prevents pigmentation in certain areas (see Onslow, page 91). There is a considerable influence of nongenetic factors on the variability of the character, studied especially by Wright *et al.* in guinea pigs. There is further the fact that pigmentation in these cases is dependent upon the temperature and may be changed considerably, especially in the so-called *Dutch pattern* of pigmentation of the tips (ear, nose, feet) by temperature action. Actually, exposure to cold leads to pigmentation of otherwise unpigmented parts (W. Schultz, see page 155). There is a considerable amount of genetic modification of the pattern, *i.e.*, the extent of the white areas. Modifying genes may be accumulated by selection and result in almost self-colored or almost white condition. (Most of the literature is found in the papers of Castle, Wright, Dunn). In a recent paper, Dunn and Charles (1937) showed that, in mice at least, other genes for spotting exist, which cannot be called modifiers, because in the absence of the main gene they also cause spotting. These give a combination effect with the main gene, and the cumulative action of the different spotting genes determines the phenotype. This, then, is a case of multiple-factor action, known in innumerable cases of quantitative characters and mentioned above also in connection with pattern types in the case of the nun moth (page 128). In the mouse case, this cumulative action may appear phenotypically as a change of dominance of the main gene: S/s (s is the recessive spotting gene) is Wild type; in the presence of another spotting gene (of the K -group), spotting is somewhat dominant. Of course, this is not a shift of dominance but an additive effect visible also in the heterozygote.

These facts lead to the following deliberations. The interaction of different genes in controlling the phenotype may oscillate between two extremes.

1. The genes in question exercise their main effects upon different reactions which do not interfere with each other. In this case, the phenotype will show a combination of the different traits involved. Such cases have been worked out quantitatively by Csik (1934a) for wing characters in *Drosophila*, many of which may be independently combined without interfering with each other. Such an effect may occur on the basis of qualitatively different reactions or in connection with actions at different times. But it is probable that such cases will prove to be rather rare (in

spite of the immense literature upon simple recombinations of genic effects) if thoroughly investigated, because it is highly probable that somehow a change in developmental reactions caused by a mutant gene will create a situation that affects also the workings of simultaneous or consecutive processes.

2. All transitions will be found from such a situation to the other extreme, *viz.*, that the reactions caused by different genes act directly or indirectly upon the same process. An indirect action would occur, for example, if one gene-controlled reaction changed the pH value present when the other gene-controlled reaction occurred. A direct action might be of various types as follows:

a. One reaction produces a substance necessary for some morphogenetic process; the other, another substance with the same type of action, *e.g.*, two different types of growth hormone.

b. Both reactions affect different developmental processes, involved in the formation of the phenotype; *e.g.*, one increases the rate of cell division; the other, cell growth; and their effect upon size is therefore additive.

c. Both reactions have an identical effect, reached possibly by different means; *e.g.*, a definite substance is as well produced by oxidation of something as by reduction of something else. The result again would be additive.

d. The different genic reactions affect different phases of general developmental processes; *e.g.*, one changes growth in length; the other, growth in width; the result might be additive, but it might also be a compromise between both effects.

Other possibilities may easily be visualized. In a general way, we may therefore expect interactions to be either combinatory or additional or of the nature of a compromise or of a combination of these three possibilities. The actual effect will depend upon all those variables of gene-controlled reactions that have already been described, *viz.*, velocity of the main reaction, threshold values, time of final determination, time of onset of different decisive reactions. Examples for such interactions may therefore be found at many places in former chapters.

A systematic attack upon these problems has been made also in *Drosophila*. Schultz (1929) used the so-called Minute dominant mutations. (As a matter of fact, many if not all of these are actually deficiencies; for the present discussion, the nature of the

gene in question is irrelevant.) They are lethal when homozygous; and all of them, scattered over all chromosomes, have a similar phenotypic effect, *viz.*, shorter bristles, blunter wings, plexus venation, smaller size, slow development, larger and rough eyes, poor viability. Schultz argued that a combination of two Minutes ought to give a lethal effect or at least an extreme phenotype if all are concerned with the same primary reaction, *i.e.*, ought to give an additive effect. No combination gave such a result. To test whether an all-or-none or threshold effect was involved Schultz made experiments that led to the following observations:

1. A duplication suppressing a known Minute effect at the same section of the chromosome does not influence another Minute effect at a different locus.

2. One Minute is recessive to two normals in triploids. Two simultaneous but different Minutes do not change the situation.

3. Two of the same Minutes in a triploid, however, are lethal.

From such facts Schultz concluded that no threshold effect can be involved and the different Minutes do not affect the same primary reaction. He then combined different Minutes with different allelomorphs of Delta, which has a phenotypic effect that is roughly the contrary of Minute. A combination Delta-Minute is either an extremely abnormal individual or lethal. This effect varies quantitatively in proportion to the effect of the Minute involved. And it varies also in proportion to the grade of the Delta allele; the highest alleles produce, in this combination, lethality; the next lower one, early death of the thoroughly abnormal fly; the next lower one, later death; and the lowest member, an abnormal fly not capable of hatching. Similar effects were produced in combination with other genes, showing that the effect of the Minutes concerned in these results (the secondary reaction of Schultz) is quantitatively different in a definite seriation of Minutes. This applies to measurable characters like viability and bristle length within the series of Minutes and the parallel series of combinations with other genes. Schultz accounts for these facts by the assumption that a reaction exists in development, in which a great many genes are involved; and that changes in any of these contributors may set off a secondary reaction, the Minute reaction. This would then illustrate one of the possibilities of genic interactions, as outlined

above. But it ought to be added that the destructive effect upon the development of practically the whole organism sets aside such dominant mutations from what is ordinarily called a gene mutation. It will be wise at present to be cautious about drawing conclusions from such cases as Minutes, Deltas, etc.

Dunn and Coyne (1935, 1937) have carried the same problem a little further. They selected Minutes that show an increasing series of retarding effects upon development, the descending series being *Mw—Mb—Mz—Mh—ML₂*, which meant an average delay in the larval period from 3 to 1 days. These Minutes were combined with mutant genes reducing the eye size, under the assumption that a decrease of eye size means a change in the relative growth rate between eye and body. In these combinations with the Lobe mutant, the eye size was actually reduced, and in addition the grade of the reduction paralleled the foregoing series for the growth-retarding effect of the Minutes. Apparently, in this case the interaction effect of Minute and Lobe is clear: it is the growth-retarding influence of the Minute reaction that interferes with eye development of Lobe, pointing to a similar effect of both "genes," which becomes additive.

A corresponding piece of work has been accomplished with the eye-color mutants of *Drosophila*, though no actual quantitative work has been published thus far. The many genes for eye color situated at different loci have been bred in many combinations showing their interaction. In a general way, it may be said that combinations of two colors are at least as light as the lighter one and frequently lighter. Vermilion and garnet, for example, give together a yellowish red. Other combinations of two colors appear white. (The same has also been found by Whiting, 1934, in *Habrobracon*.) Attempts at further analysis in terms of genic products have been made by Wright (1932), Crew and Lamy (1932), Schultz (1935), and Ephrussi and Beadle (1937). Wright noticed that the double recessive of scarlet and brown, neither of which changes the eye color very considerably, is white. Scarlet and vermillion produce together a color like vermillion. From which it might be expected that vermillion and brown together would produce white, which is the case. Wright thinks that the vermillion and scarlet genes are concerned with two different links in the same reaction chain, whereas brown may have to do with a qualitatively different

process. Crew and Lamy (1932) found a similar case in *Drosophila obscura*. There is an autosomal recessive purple which acts upon vermilion as a modifier of dominance. The double recessives are again white, as in Wright's case and as in the apricot-ruby combination mentioned by Agol (1931). Crew and Lamy think that the result is to be explained on the basis of different times of action of the two genes: Vermilion causes premature cessation of pigment production; purple, a delay in starting the processes, which, combined, means no pigment production. We have reported (page 33) on the work of Schultz who found that the eye colors fall into distinct groups regarding the earlier or later onset of pigmentation. Brown belongs to the group of fast formation of pigment; vermilion and scarlet, to the slow group. In the combinations that Schultz made (the complete data have not yet been published), he expected that members of the same group which are supposed to affect the same reaction should in combination not show much difference from the effect when single. Members of different groups, which are concerned with relatively independent reactions, when combined should show marked differences from either individual effect. In development, deposition of pigment should begin at the time characteristic for the earlier component. The type of pigment should be determined by the later formed pigment. As an example, Schultz mentions the combination vermilion-sepia. It has much pigment in the primary cells, little below the basal membrane, like vermilion. The color of the pigment is yellow, as in sepia. Schultz reports that 100 such effects have been studied and found to conform to the rule, on the basis of two independent reactions involved. The interactions are summation products of independent reactions: each gene does its own job. But obviously this cannot be the whole story, as the preceding case of vermilion-brown = white indicates.

On page 186, we shall describe the results obtained by Ephrussi and Beadle with eye transplantation in *Drosophila*, demonstrating in some cases the existence of substances acting at a distance. These investigators postulated two such substances (with a recent addition of a third one) involved in Wild-type color, *viz.*, cn^+ -substance, which is missing in a cinnabar fly; and a v^+ -substance, a vermilion fly being deficient in both. Vermilion and cinnabar disks in Wild type, therefore, develop Wild-type color, whereas

other eye-color types develop their own color after transplantation. But vermilion and cinnabar disks grown in claret, carnation, and a few other mutants develop either vermilion or a color between this and Wild. The authors (1937c) then proceeded to test eyes containing two recessive colors, one being vermilion. It has been mentioned previously that vermilion-garnet is yellowish. This would mean that there is a considerable insufficiency of v^+ -substance, which could be tested in appropriate transplantations. The results were:

1. Eye disks of double recessives, one being vermilion, implanted into Wild-type hosts. In all cases, the color was that of the other mutant (not vermilion).

2. Eye disks of the second mutant implanted in vermilion hosts. Some develop their genetic color; others, a lighter color; and some, a much lighter color; but none so light as the double recessive. (There is also a sex difference.)

3. Eye disks of the different mutants transplanted into hosts double recessive for the same mutant and vermilion. The results are parallel to those under 2.

4. Young Wild-type disks implanted in older vermilion hosts developed intermediate pigment.

The first set of these experiments agrees with the assumption that the Wild-type host furnishes the missing v^+ -substance without which no vermilion develops. In the second group, wherever the genetic color appeared, the implant must itself contain the necessary v^+ -substance; where, however, lighter colors appeared, the mutant eye could not have a sufficient amount of this substance. The third group shows the same thing, but it is surprising that the double-recessive host does not supply any v^+ -substance, which ought to be produced by the nonvermilion gene. It is probable that such experiments will lead to further insight if put on a quantitative basis. The present situation is conceived by Ephrussi and Beadle (1937b) in the following way: When a Wild-type eye disk is grown in a mutant host and develops the mutant color, a substance is supposed to be lacking or deficient that is needed for Wild-type development. By checking different combinations against each other, three such substances have been found which were called v^+ (missing in vermilion), cn^+ (missing in cinnabar), ca^+ (missing in claret). These substances are supposed to be formed

as steps in a chain reaction in the order $ca^+ \rightarrow v^+ \rightarrow cn^+$. ca^+ is assumed to be formed first because it is present in full concentration in flies lacking v^+ , cn^+ , or both.¹ It reaches effective concentration before puparium formation; v^+ , however, only later. V^+ is supposed to be formed prior to cn^+ because (among other facts) a v -implant, deficient in cn^+ -substance if grown in a cn -host (with the same deficiency) gives Wild eye, thus proving its ability to produce cn^+ . In the production of these three substances, a large number of genes is concerned. For the first step no other gene but ca could be found to be effective. The facts mentioned above for the transplants of many mutant disks into v -hosts show that a number of these genes are concerned with the production of at least the v^+ -substance, *e.g.*, pn , pr , sf , etc., partly in the eye, partly in the body, *e.g.*, v , p , rb . Cases in which cn -implants are only partially affected by the mutant host indicate genes concerned with cn^+ -production; bri and mah are mentioned as such. It is clear that thus far these relations cannot be expressed in concrete terms. A general description would probably again assume the form of the theory of reactions in tune.

In other chapters, we reported the considerable amount of quantitative work done with the Bar locus in *Drosophila*. Hersh (1929), who pushed the analysis furthest, has also used this material for an attack upon the problems of this chapter. He took a selected homozygous stock of Bar, supposed to be freed of heterozygous modifiers, as a basis and studied the effect of other mutant genes in the X-chromosome upon facet number. For obvious reasons (one X), the males only were used for the counts. Hersh took into account also another set of facts, to be reported below (page 215), *viz.*, the different growth rate of the dorsal and ventral eye lobes, which follow the equation for heterogonic growth (see page 216): $Y = bX^k$, in which X and Y are the facet numbers in the dorsal and ventral lobes; b the size ratio of the lobes at the time of facet formation, *i.e.*, the initial difference; and k the ratio of the logarithmic rates of facet formation. The results of this inquiry are summarized (in simplified form as compared with Hersh's table, 1929) in Table 20, which compares facet numbers of a forked Bar line with those after

¹ Recent work shows ca^+ and v^+ to be identical. The seat of production of the substances is eye, fat body, Malpighian tubules.

addition of the genes *scute*, *echinus*, *crossveinless*, *cut*, *vermilion* *garnet*, and also the calculated values of *b* and *k*.

TABLE 20
(From Hersh)


Genotype							Difference in facet number from pure <i>fB</i> line	<i>b</i>	<i>k</i>
<i>sc</i>	+	+	+	+	+	<i>f B</i>	+ 0.26	0.22	1.24
+	<i>ec</i>	+	+	+	+	<i>f B</i>	+ 4.87	1.05	0.85
+	+	<i>cv</i>	+	+	+	<i>f B</i>	+23.94	3.18	0.61
+	+	+	<i>ct</i>	+	+	<i>f B</i>	-15.28	1.24	0.80
+	+	+	+	<i>v</i>	+	<i>f B</i>	+18.51	0.24	1.17
+	+	+	+	+	<i>g</i>	<i>f B</i>	-24.32	1.20	0.79
+	+	+	+	+	+	<i>f B</i>	0	0.37	1.11
<i>sc</i>	+	+	+	+	+	<i>f B</i>	+ 0.26	0.22	1.24
<i>sc</i>	<i>ec</i>	+	+	+	+	<i>f B</i>	+ 5.54	0.50	1.02
<i>sc</i>	<i>ec</i>	<i>cv</i>	+	+	+	<i>f B</i>	+23.48	0.89	0.91
<i>sc</i>	<i>ec</i>	<i>cv</i>	<i>ct</i>	+	+	<i>f B</i>	+52.18	2.28	0.71
<i>sc</i>	<i>ec</i>	<i>cv</i>	<i>ct</i>	<i>v</i>	+	<i>f B</i>	+58.06	2.14	0.73
<i>sc</i>	<i>ec</i>	<i>cv</i>	<i>ct</i>	<i>v</i>	<i>g</i>	<i>f B</i>	+ 2.73	1.95	0.75
+	+	+	+	+	<i>g</i>	<i>f B</i>	-24.32	1.20	0.79
+	+	+	+	<i>v</i>	<i>g</i>	<i>f B</i>	-17.11	0.49	1.07
+	+	+	<i>ct</i>	<i>v</i>	<i>g</i>	<i>f B</i>	-16.08	0.90	0.88
+	+	<i>cv</i>	<i>ct</i>	<i>v</i>	<i>g</i>	<i>f B</i>	- 7.65	2.49	0.66
<i>sc</i>	<i>ec</i>	<i>cv</i>	<i>ct</i>	<i>v</i>	<i>g</i>	<i>f B</i>	+ 2.73	1.95	0.75

This table shows that some mutant genes increase, others decrease, the Bar action and are, in Bridges' terminology, plus or minus modifiers. If more than one are involved, the action might be cumulative or only of the same type as with one of the members. The same gene may even act in one combination as a plus and in another as a minus modifier. The values of *b* and *k* are influenced in a similar way. There is no relation between the normal, known actions of these genes and their actions in these combinations. But the facts as a whole seem to me to indicate that the reactions controlled by these mutant genes are primarily of a quantitative type, shifting the velocities of some processes in one or another direction, and that the time relations of these and

the Bar reaction will influence the effect of the Bar reaction by \pm changing its time of onset, its speed, its end or threshold value. In short, these facts again fit best into a general picture of the type as expressed in the theory of reaction velocities in tune.

Interaction of genes, in the cases reported, was analyzed by a comparison of the phenotypes, though the reactions leading to these phenotypes were more or less inaccessible. In plants, an analysis is available which is based upon the study of the chemism of the process, *viz.*, the work of Lawrence and Scott-Moncrieff (1935) on flower color in Dahlia. We have reported (see page 95) the chemical side of this work. A special study was made of the interaction of the different genes controlling the chemism of flower color. (This is the work alluded to in connection with dosage differences in polyploids, page 150.) The genes in question are as follows: *A* is necessary for light anthocyanin color produced by either cyanin or pelargonin. *B* is needed for heavy anthocyanin pigmentation. *I* produces ivory flavone and *Y* produces yellow flavone. As these Dahlias are tetraploid, each factor is quadriplex. *Y* and *B* are completely dominant in simplex condition; *A* is cumulative from simplex to quadriplex. *I* is incompletely dominant; when simplex, it produces very little pigment; when duplex to quadriplex, the complete amount of pigment. A fifth gene *H* acts as an inhibitor of yellow flavone, with a cumulative effect in the four quantities leading to cream and primrose colors.

The interaction of these factors is, generally speaking, such that the pigments suppress each other, but the flavones suppress the anthocyanin more than vice versa. The degree of suppression depends upon the total number and the proportion of the flower factors present. We may choose a few examples from the large array of facts. Anthocyanin intensity (by *A*) is diminished, when ivory flavone (by *I*) is present, less pigment being actually present. If the number of these genes is changed (1 to 4), the effect is proportional; *e.g.*, more *I*-genes increase the paleness of the color by proportionally reducing the amount of anthocyanin formed. The relative effect of *I* is higher than that of *A*, as the combinations of different quantities of both show. The following grouping from low to high anthocyanin color (left to right) in different combinations of *A* and *I* in 1 to 4 quantities illustrates the point:

Little or No Anthocyanin	Less or More Anthocyanin →			
				
A_1I_3	A_1I_2	A_2I_3	A_3I_4	A_4I_4
A_1I_4	A_1I_1	A_2I_2	A_3I_3	A_4I_3
A_2I_4	A_1	A_2I_1	A_3I_2	A_4I_2
		A_2	A_3I_1	A_4I_1
			A_3	A_4

In the same way, the other combinations were analyzed. Y acts strongly upon both I and A , suppressing them completely in some combinations; Y and I similarly suppress the action of B ; the action of I changes the effect of B to the type of an A effect. Also, in these cases, the cumulative effect of the quantities of the respective genes is observed. But it is not simple and appears only in definite combinations, in which the potential cumulative effect of a gene becomes an actual one; *e.g.*, B is completely dominant and has alone therefore no actual cumulative effect. But when the B effect is changed by the presence of Y , the cumulative effect appears. (This shows, of course, that a threshold problem is involved, as in so many instances discussed above.)

This potential and actual cumulative action as well as the interaction in the form of suppression of the coproduction of other pigments may be interpreted in terms of the chemistry of pigment formation. (See page 96 for the basic chemical facts.) As a balance of the different pigments is clearly involved, the authors conclude that all pigments are being produced through some common fundamental chemical reaction or from some limited common source from which all pigments are derived and for which they compete. (See the similar conclusions of Wright, page 157.) The supply of this source must be so limited (see threshold, page 158) that the quantity of each pigment can increase only at the expense of the others, depending upon the relative quantities of the factors present. This hypothesis was tested by a quantitative comparison of different combinations in extracts, from which the relative demands of the factors upon the common source was estimated. It was found, for example that in BY -types both pigments are produced from a source that must be three times as great as the maximum source in the AI -types but smaller, when all four genes are present.

On page 96, we mentioned the fact that anthocyanin may be cyanin or pelargonidin. But in *Dahlia*, *A* and *B* do not control one or the other; rather the whole quantitative system of the genes involved determines this alternative. Pelargonin production, for example, depends upon the following factorial proportions:

1. *A* or *B* together with *Y*.
2. Two or more *B*.
3. One or more *B* together with three *I*.
4. One or more *B* together with two or more *I* and at least one *A*.
5. One or more *B* together with one *I* and at least three *A*.

The whole body of these facts is summed up in a quantitative representation based upon the arbitrary assumption that the limit of pigment source that can be made available in *Dahlia*, whatever factors are present, can be expressed as six units. The potential units of the different genes are then calculated in the following way: *B* and *Y* are capable of using the maximum source in simplex condition and therefore contribute at least six potential units. *A* has a cumulative potential value which in quadriplex condition is less than or equal to the maximal source. Following this way of estimation, unit values fitting the facts are fixed as $Y = 9$, $B = 6$, $I = 1$, $A = 1/2$, and their combined action would be, in a few examples, if 8 is the threshold value for pelargonidin:

$$\begin{array}{lcl}
 A_4I_4 & = & 6 \text{ units} \\
 B_1A_2I_1 & = & 8 \text{ units} \} \dots\dots\dots \text{Only cyanin} \\
 A_1Y_1 & = & 9.5 \text{ units} \\
 B_1A_1I_2 & = & 8.5 \text{ units} \} \dots\dots\dots \text{Only pelargonin} \\
 B_2 & = & 12 \text{ units}
 \end{array}$$

Thus the entire body of evidence leads to the following conclusions:

1. The potential unit values of the four color factors are as given above.
2. A sum total of six units is sufficient to produce the maximum pigment source that plants carrying *B* or *Y* are capable of supplying. In *AI*-plants, this maximum is two units.
3. Each dominant factor may contribute to this source according to its potential unit value. But the actual units are limited to 6 (or 2) whatever the potential units.

4. Each factor competes for this source in terms of its potential units. The total pigment production depends upon the proportion and power of interaction of all factors.

5. *Y* governs production of yellow flavone; *I*, the ivory flavone apigenin. *H* reduces the potential value of *Y*.

6. In the presence of *A* and *B*, cyanin is produced if the total potential units are below 8; and pelargonin, if they are above 8.

7. Tentatively these actions in terms of units are related to the constitution of the pigment molecule by assuming that they are involved in controlling the oxidation of the phenyl ring.

There is no doubt that in this fine piece of work a considerable step has been made toward interpreting the interaction of genes in terms of the interplay of chemical reactions. In doing so, the same types of principles were found at work as in the other cases that we reported: reaction velocities, proportional effect of gene quantities, threshold conditions, competitive actions (see sex-determining reactions, page 52). The system of genic action here revealed is then the same as postulated in Goldschmidt's theory of reaction velocities in tune, as the authors also indicate.

We may state finally that it would be desirable to have more information regarding concrete types of reaction and the exact nature of their interplay. What little is known in this respect will be reported in a special chapter. Attention should be called finally to some cases in which the disturbance of the proper tuning of reaction can be described in relation to definite processes. Goldschmidt has discussed, in a number of papers since 1920, the many beautiful examples of this kind furnished by the facts of intersexuality. The simplest and clearest is the following: The end of morphogenesis of the organs of insects is given by the process of chitinization of the soft organs, and normally this occurs when development is completed. In intersexes, numerous organs start development at a later date than normal, with the consequence that at the time of chitinization a developmental stage or even an imaginal disk is present where a completely developed organ should be. In this case, the embryonic structure is being chitinized and appears thus in the adult. Here the effect is produced genetically by the improper balance of the reactions controlled by female and male determiners together with the unchanged general reactions of development. It is an actual disturbance of tuning.

There is another case that has also been frequently discussed in Goldschmidt's writings—the abnormality called *prothetely*. In these cases, which at least sometimes are caused genetically, a single organ or a few organs are ahead in development. Most typical are the cases in insects, where a caterpillar forms pupal antennae (see Goldschmidt, 1923*b*) or pupal wings (Tenebrio, Ferwerda, 1928) (Fig. 33). As it is known now that the evagination of the imaginal disks is under hormonal control, this means probably that in these cases the threshold has been lowered locally. In any case, there is some disturbance of reactions that are normally definitely tuned and that have to do with hormonal control of developmental processes.

There can be no doubt, then, that the combined action of the genes in controlling developmental processes occurs in the form of a system of gene-controlled reactions, which have to be in proper tune to work together harmoniously. A definite stuff, a definite physical or chemical property of the cytoplasmic substratum, must be present at a definite time and place to make the proper course of other reactions possible. This interplay of reactions in tune is the physiological process, which is meant (or ought to be) when one speaks of genic balance or of all the genes taking part in all determinations. There is much loose thinking in this field.

One has, for example, argued as follows: There are so and so many genes known to influence the eye color in *Drosophila*. Therefore so many times more genes must be involved in the determination of an eye, and so many more for the whole normal development. The proper argumentation would be: Numerous reactions are involved in orderly development, including also the development of the eye and its details. As the formation of eye pigment in definite cells is a chemical process which is dependent upon a number of chemical and morphogenetic situations, which in their turn are dependent upon



FIG. 33.—Case of *prothetely*. Caterpillar of *Lymantria dispar* with pupal antennae. (From Goldschmidt.)

many others, it is to be assumed that mutations that change reactions that have to do with any of these processes in the end can also affect eye pigment. It might just as well be that 1 or 100 per cent of the gene-controlled reactions will have such an effect, if tampered with by a mutation.

8. THE TYPE OF REACTION CONTROLLED BY THE MUTANT GENE

The facts thus far discussed point to the conclusion that mutant genes act by changing rates of processes concerned with the harmonious progress of development. Many of the authors quoted in this connection have tried to formulate concrete ideas concerning these reactions. In so far as these ideas are of a more speculative type regarding the nature of the gene, they will be mentioned in a later chapter. In this chapter, we intend to study those facts which actually demonstrate processes that permit one to link the insight into the action of the mutant gene with such insight as we have concerning the factors of development.

A. REACTIONS WITHIN THE CELLS

A priori, two types of reactions controlled by mutant genes are imaginable, if we do not consider the nature of the product of reaction but only the dynamics of its production. One possibility is that the gene-controlled process is confined to the cells in which the mutant gene is situated. In terms of experimental embryology, this would be a self-differentiative type of process. The other type of reaction would be the production of substances that spread from a center of origin over parts of the developing embryo. In terms of experimental embryology, this would be a process of the type of dependent or inductive differentiation. It is very difficult to prove whether or not the first type exists at all. The only possibility of attacking the problem in genetic experimentation is the study of mosaics of genetically known constitution, which appear either as freaks or regularly in certain strains. The work of Morgan and Bridges (1919), Patterson (1929*a*), Sturtevant (1929), Demerec (1928), and others has furnished important facts. If a *Drosophila* egg starts development as a female, with two X-chromosomes, it was shown by Morgan and Bridges (1919) that one of these X's is occasionally eliminated from a cleavage nucleus. These cells will then be male, and the result is a gynandromorph. (There are other modes of formation

of gynandromorphs—see Goldschmidt, 1931*d*—but they do not furnish much information for the present problem.) If mutant genes are present in the X-chromosome, the mosaic male spots will also show the mutant character, and the facts showed that the development of these is autonomous. Even very small mosaic parts behave as if they were independent of the rest of the animal. In these cases, then, the mutant genes must have acted within the cells in which they were located, and their action may have begun rather late in development. But it ought to be emphasized that the characters involved here are such as are actually formed only at the end of differentiation within the cells, *e.g.*, pigment formation or development of bristles. Developmental processes that have to do with growth and differentiation of a whole *Anlage* do not seem to react within the individual cells; in mosaics, they appear only in a whole organ. This applies, for example, to wing form.

These facts, derived from sex mosaics, reappear in cases where mosaics have been produced in different ways. There are genes like the Claret gene in *Drosophila* (Sturtevant 1929), or the Minute-*n* gene (Bridges 1925), which produce elimination of chromosomes and therefore mosaics. There is the possibility of producing a similar result by inducing somatic mutations by X-ray action upon individuals that have been marked by definite genes, preferably by heterozygous sex-linked genes. A special study has been made by Patterson (1929*a*) using eye colors in *Drosophila*. The results coincide with those found in other cases of mosaicism, *viz.*, that mosaic areas may be formed from a whole eye down to a single aberrant ommatidium. The genic effect upon pigment formation then appears rather localized (see page 176 for more facts). Here it was also possible to perform the important experiment of producing the somatic mutation at different times of development. The result was, as expected, that the earlier the treatment the larger the mosaic area.

A third method of attack upon the same problem is furnished by the study of what has been called *unstable genes*. In this chapter, we are not concerned with the explanation of this phenomenon but with the results. It is assumed that in these cases mutant genes have the tendency to revert to the Wild-type (or, more rarely, if ever, to another) allelomorph during development. The result is a mosaic spot of different tissue, the size

depending upon the time in development in which the *somatic mutation* takes place. This phenomenon is rather frequently found in plants, especially in regard to colors but also affecting other morphological characters. Demerec (1935b) counts 63 such characters in plants, especially studied by Emerson, Baur, Demerec, and Imai (see Demerec 1935b). In animals, only a few cases are known, most of them reported by Demerec (see Demerec 1935b) in *Drosophila virilis*. Here a body color is involved, and the miniature wing. (We mention the important point—see page 212—that the miniature wing is a complete wing which did not finish the pupal phase by growth of the individual cells, *i.e.*, by a very late process in development.) In all these cases, the existence of rather small mosaic spots shows that the mutant gene acted within the cells in which it was situated.

There is a fourth type of evidence of the same order. Stern (1936) studied mosaic spots that were produced by somatic crossing over which occurred in small groups of cells. In this case, also, very small spots were involved, which showed genic action within individual cells of such an organ system as the skin. Demerec (1934a) used a somewhat different method. He also bred mosaic flies in which the mosaic spots were the results of somatic segregation. These mosaic spots had been marked by an ingenious method with small deficiencies (lack of a piece of the chromosome at a definite locus); and as they arose by somatic segregation, there were always adjacent twin spots with and without the deficiency. Those with the deficiency will be missing if the deficiency is lethal for the cells that carry it. The size of the spot, of course, measures the time at which somatic segregation occurred. Of 33 deficiencies in the X-chromosome thus tested, all but one were lethal to the cells. This, of course, shows only a general effect and does not contain information regarding the time of action of a special gene-controlled process.

These facts certainly show that many gene-controlled reactions may be confined to a single cell, and it is possible that this type of process is typical for some gene-controlled processes that take place late in development and are localized in groups of identical cells, without a pattern within this group. But even in these cases a certain centrifugal action away from the cells containing the mutant genes has been observed.

Sturtevant (1927) produced mosaics of the Bar-eye mutant of *Drosophila* with normal eye facets marked by color genes, by introducing the Minute-*n* gene which has a mosaic-producing effect, as mentioned above. He showed that mosaic spots of Nonbar tissue situated in the periphery of the area of the would-be normal eye are prevented from forming facets. Near the Bar area, however, and in close contact with mosaic Nonbar tissue, facets may be developed also in Bar tissue. The adjacent normal tissue then exercises a facet-forming influence upon tissue that would be unable to develop facets by the action of the genes within its own cells. Sturtevant himself assumes that here an influence beyond the cells containing the genes (an induction) is seen, though he mentions also the alternative that a time relation might be involved, *viz.*, a difference in regard to the time at which the formation of facets is determined in different areas. Huxley (1935c) has proposed a somewhat different explanation in terms of growth rate, which however also requires a growth-stimulating influence of normal on Bar tissue. (See also the work of Huxley and Wolsky (1936) reported on page 33.) A similar case is reported by Sturtevant (1932). He compared mosaic patches of the mutant scute, which removes certain bristles in *Drosophila*, with all-scute flies and finds that this scute effect is smaller in little mosaic patches, indicating the possibility of an influence of the normal surroundings on the mosaic spots. Another similar case is found on a gray body with yellow mosaic spots which are less yellow and less distinct than typical yellow. Finally, a case ought to be mentioned that was described for *Habrobracon* by Whiting, Greb, and Speicher (1934), and A. R. Whiting, 1934. They produced eyes with mosaic spots from binucleated eggs. Whenever any color from the orange locus is associated in a mosaic with one of its alleles, no sharp line of separation is found between the two, but continuous shading. When, however, the white locus is involved, there is a clear-cut mosaic. Adjacent cantaloupe and ivory tissue form a black stripe in between, showing that from both spots reciprocal stuffs diffuse which produce pigment when combined.

Of significance in this connection also are the remarkable facts found by Haberlandt (1935) in the chimeric *Crataegomespili*, which have a skin of one and a core of the other species. The palisade tissue, derived from *Mespilus*, is intermediate in char-

acter; and the *Crataegus* epidermis shows a clear influence of the underlying *Mespilus* tissue. The structure is actually more intermediate than in real hybrids. If from such a chimera pure *Mespilus* shoots are formed, containing only *Mespilus* cells and chromosomes, an influence of the *Crataegus* genotype is visible and persists. No doubt in this case morphogenetic stuffs, controlled by the genes of one species, pass from cell to cell and act upon the distant cells.

None of these cases is yet quite clear, and at present it may suffice to register the facts.

There can be no doubt that some gene-controlled reactions take place within the same cells in which the respective genes are situated; furthermore, that this action may take effect even if it is started rather late in development. It seems, moreover, that this type of genic action is confined to such reactions as occur either at the very beginning or at the end of development and that in the latter case they lead to no further pattern formation. In some cases, however, the products of these reactions may diffuse into the surrounding cells.

In his work on sex, from which Goldschmidt originally had derived his view on genic action, he thought that he was dealing with a typical case of purely intracellular action of the genes in question. Embryological and morphological facts which were found later convinced him, however, in agreement with the experimental work of Seidel (see Seidel, 1936), that in insects, also, a part of the determinative reactions are not of the intracellular, strictly self-determining type. We shall mention these facts later. The foregoing discussion shows that such types of action are to be expected wherever pattern formation is involved.

It has to be kept in mind also that in experimental embryology, the limits between self-differentiation and induction have turned out to be rather vague, if not actually nonexistent, and that the actual difference is a difference in time of irreversible determination. But there are also some cases existent in which the determinative reaction, controlled by genes, actually takes place within highly differentiated cells without induction from cells in the neighborhood. Such cases may be analyzed in the mosaics that the experimenter produces by transplantation as well as in the genetic mosaics reported above.

As an example of this type, Twitty's recent work (1936) on newts may be mentioned. He transplanted the parts of the embryo that produce the pigment cells reciprocally between different species of *Triturus*, which are characterized by a different arrangement of their pigment cells. The transplants kept the arrangement of the species from which they came. An example of the interactions of both types of differentiation is the well-known experiments of Spemann, Schotté, Holtfreter, *et al.* The differentiation of the region around the amphibian mouth is of the inductive type. If the inductor is taken from a Triton, and the tissue to be induced from a frog, the inductor induces differentiations of mouth organs, but the specific type of organs (horn teeth, etc.) is controlled by the genes in the induced tissue.

As far as experimental information goes, we may assume that in vertebrates the inductor type is more frequent in development; in insects, however, self-differentiation is more frequently met with, though not so exclusively as was believed a few years ago. (Embryological work of Seidel and students; inferences from genetic work as reported here.)

Thus far, we have considered only such gene-controlled reactions within the cells as occur at the end of development. But the majority of hereditary reactions occurring within one cell are those occurring within the animal egg in its first stages of development. In a later chapter, in which the problem of pattern will be treated, we shall discuss the problems connected with the early differentiation of the egg, and we shall mention the cases in which genes are known to interfere in this process. As yet there has been, in general, no genetic analysis of these intracellular rearrangements of area with restricted determination (organ-forming stuffs, embryonic fields, etc.) which occurs in the one-cell stage of the eggs of determinative type and continues through early development. The only point known is that these processes are hereditary and specific and that they may occur with different speeds in nearly related species. The geneticist cannot doubt that such processes of distribution and arrangement of cytoplasmic components occur under control of the genes. The work of Haemmerling, which will be reported on page 192, has proved such control at least for a complex plant cell, and the author is in agreement with him when he extends his conclusions to the developing egg. Experimental embryologists,

however, speak of the same processes usually as being of a cytoplasmic type. This is not correct, since all the facts indicate that the same type of processes may occur either later in development or earlier and even in the undeveloped egg cell (see page 206). This misleading description becomes dangerous when facts are analyzed to show the part played by the maternal cytoplasm in early development as compared with the influence of the genes contributed by the sperm. If it is found that certain developmental processes occur under complete control of the egg, this does not mean that these processes are not under control of genes. It means actually that certain genes present in the egg nucleus control the pattern formation in the egg and in the following stages. In a hybrid egg, therefore, such a pattern ought to be of a hybrid type, if the parents had different patterns. But this experiment has thus far not been performed. As a type of analysis of the first generation, we mention Hamburger's recent work on species hybrids in amphibia (1936). He crossed *Triturus cristatus*, *T. taeniatus*, and *T. palmatus* and followed in detail the development of the hybrids. In this case, the parental forms are different only in the later embryonic stages, the tail-bud and early larval stages. Up to a somewhat later stage, the limb bud stage, the embryos are absolutely maternal in reciprocal crosses, and only later the influence of the father becomes visible in influencing growth and pigmentation. This shows, then, that a certain amount of pattern formation before as well as after fertilization occurs under the exclusive influence of the egg-nucleus genes. In terms of intracellular gene action, it would mean that there is no difference between the diffusion through the cell of substances produced by action of the genes (with consequent arrangement as in a pattern) and the diffusion of these substances from cell to cell. Embryonic effects of genes and other effects of the usual type are hardly different in principle (see also page 205).

We may point out finally that diffusion of gene-controlled products from cell to cell may become visible in quite a number of cases in which these products have only a general action. Baltzer and de Roche (1936) discussed this problem in connection with their experiments on growth of merogonic tissue upon a different host (see page 268). Here the otherwise impaired vitality of the merogonic cells is reconstituted, and this might be interpreted on a genic basis as a check to lethality by diffusion products

from the surroundings. But since Ephrussi (1935) has shown that tissue containing homozygous lethals may be grown in tissue culture, it might also be possible that an influx of some product controlled by the normal chromosomes is not involved in Baltzer's case but rather a draining off of poisonous products of abnormal metabolism. In agreement with this interpretation is also the fact that Hadorn (1934) was able to grow merogonic cells in tissue culture.

B. REACTIONS OF AN INDUCTIVE TYPE

The experiments just mentioned lead to the type of embryological process called *induction*. A number of facts are known that prove that the products of gene-controlled reactions are formed in definite areas of the embryo at a definite time and spread hence into neighboring territories where they induce certain morphogenetic processes. These facts constitute the most direct link between genetics and embryology.

1. Terminology.—When Goldschmidt (1920*b*) tried to derive general ideas on gene action from his experiments in intersexuality, he had to face the following situation. It was proved that sex was controlled in *Lymantria* by male and female reactions of definite velocity which are timed in such a way that one or the other passes the threshold. Since all the facts of gynandromorphism seemed to prove that insect development is of the completely self-determinative type, it had to be assumed that the sex-controlling reactions take place within each cell, producing sex-determining stuffs. It was also known that in vertebrates, morphogenesis of sex differentiation is controlled largely by sex hormones; hence it was concluded that these intracellular sex-determining stuffs are physiologically identical with the sex hormones. The difference would be only the production within all body cells versus production in a centralized organ, the gonad. From this, the generalization was derived that all genes produce substances of morphogenetic action similar to hormones, and, therefore, the general term *hormones* was amplified in its scope to cover also such intracellular morphogenetic stuffs. When later Witschi (1929) proved that in vertebrates a special sex-determining action was exercised by cortex and medulla of the gonads whence it spread by diffusion, Goldschmidt (1931*d*) proposed to distinguish three types of morphogenetic substances

produced by the action of genes: hormones of the first order—intracellular formative or inductive substances; hormones of the second order—inductors diffusing from their place of origin and thus acting at a distance (identical with the harmozones of Gley); hormones of the third order, or hormones proper—carried by the body fluids. Meanwhile, the work of the embryologists has centered considerably around the second type of inductors; and it is necessary to use a definite terminology for the possible morphogenetic stuffs. That the term hormone was extended beyond its original meaning to cover all the types of stuffs has been much criticized. I still think that the general idea underlying this generalization is correct; but this does not prevent the use of any terminology that appears better founded.

In a recent paper, Huxley (1935a) proposed a clarification of the terminology. He points out that all transitions are found between the types of morphogenetic substances mentioned; *e.g.*, the activating substance studied by Haemmerling in the unicellular plant *Acetabularia* is, of course, intracellular, but it is shown to act by diffusion from the nucleus to the mushroom-like periphery of the complicated cell. Similar examples are cited that bridge the difference between diffusion hormones and vascular hormones. He proposes, therefore, to call all these substances activators. They may be local activators acting on the cell or tissue that produces them. These again are subdivided into intracellular activators and chemodifferentiators, the latter containing all the activators for predetermination of embryonic parts. (These may also show transitions to a type with diffusion.) The second main group is *distance activators*, or *hormones*. They are transported either by diffusion—*diffusion hormones*—or by the body fluids—*circulatory hormones*. This system is, after all, very much like that used by Goldschmidt. We shall then use the word activator in a general sense, replacing it occasionally by inductor or evocator when the embryological processes of a general type are involved; and we shall use the word hormone mostly for distance action only.

2. Genic Products of the Hormone Type.—A few facts are known that might be reported as a transitional step between the cases with a spread of a gene-controlled effect from cell to cell and a corresponding effect at a longer distance. Bonnier (1928) described a *Drosophila* mosaic in which a Bar eye on one

side made a Wild-type eye on the other side smaller (if this is the correct interpretation).

But the numbers of cases are increasing in which clear relations are found between genic action and products that act as hormones. Probably the first case outside the sphere of sex hormones was the one discovered by Sturtevant (1920) in the case of vermilion, a gene for eye color in *Drosophila simulans*. Sturtevant produced gynandromorphs in which the gonads were always vermilion in constitution if they were testes and not vermilion or Wild type if they were ovaries. When such individuals had mosaic spots of vermilion constitution in their eyes, these spots were not vermilion if ovaries were present. The Wild-type ovary then suppresses the action of the vermilion gene in the eye, or, expressed differently, the Wild-type gene present in the ovary makes this organ produce a hormone that acts upon pigment formation in the eye. (Another eye color, garnet, was not influenced by such a hormone.) This case is closely related to another one found by Dobzhansky (1931): white eye color in *Drosophila* is associated with a colorless sheath of the testis which, however, is yellow in Wild-type animals.

In gynandromorphs having the male tissues white, testes and *vasa efferentia* are transparent in young individuals, but these parts become yellow with age. If, however, an ovary is attached to male organs, the adjoining genetically white parts of the *vas efferens* soon become yellow. Dobzhansky thinks that the Wild-type gene leads to the production in all tissues of a pigment-precursor substance which might eventually reach the *vas efferens* which is able to convert it into pigment. From the Wild-type ovary, however, this substance may diffuse directly into the adjacent *vas efferens*.

A similar case was also found by Whiting in *Habrobracon* (1934). Genetically ivory mosaic spots in eyes show orange color if the gonad of the mosaic is genotypically black.

A comparable case in the flour moth, *Ephestia kuhniella*, has been worked out in considerable detail by Caspari (1933, 1935, 1936), Plagge (1935, 1936a, b, c), and Kuehn *et al.* (1935, 1936). It furnishes thus far the best known example of a gene-controlled hormonal action in development. There is a recessive eye-color mutation *aa* making the otherwise black eyes red and, simultaneously, the dark testes white. Caspari (1933) made

transplantations of testes with different combinations of the two races. When an *AA*-testis is transplanted into an *aa*-host, it remains pigmented, and the eyes of the host turn black; the result is then the same as in the two *Drosophila* cases combined. (A transplantation is, of course, another method of producing mosaics.) This primary experiment was then followed up by Kuehn, Caspari, and Plagge (1935). The genes *aa* affect, in fact, quite a number of characters in addition to eye color and gonad color: the skin of the caterpillar is paler; the color of the optic ganglia is more reddish (as opposed to brown); the amount of pigment in the larval ocelli is changed; the velocity of development and the vitality are decreased. This shows that the gene in question acts all through development. For one character, the pigmentation of the ocelli, it can be shown that a different velocity of pigment formation is involved. Probably the same applies also to the color of the ommatidia, which shows in *aa*-individuals less and lighter pigment and smaller granules. (There is also an intermediate allele a^k with intermediate effects existing.) As Caspari found, *aa*-testes transplanted into *AA*-animals became dark; *AA*-testes in *aa*-animals remain dark. *AA*-testes in *aa*-hosts make their eyes darken; but the result is not exactly the same as in pure *AA*-eyes; the quantity of pigment remains less than in the *AA*-type, and also the distribution is somewhat different. Also, if these transplantations are made sufficiently early, the larval pigment characters are influenced correspondingly. The *AA*-testis then produces a substance (or hormone) which acts all over the body. The testis is, however, not the only organ that produces this substance: implanted ovaries act like testes, though less strongly; by implantation of more than one ovary the effect is increased. The same effect, but still weaker, may even be produced by transplantation of brain. Most remarkable is finally the fact that this hormonal effect may act upon the egg cell even before fertilization: if *aa*-females contain transplanted *AA*-testes, their pure *aa*-offspring may show the early pigmentation of the ocelli characteristic for *AA*. The hormone then has entered the cytoplasm of the egg within the ovary. (We may point out that here the procedure has been reproduced that must be assumed to take place in the cases of so-called maternal inheritance of Toyama (see page 206). Especially does this last experiment show that the stuff produced

in the testis or ovary or brain by the action of the gene *A* is actually a hormone. Whether this hormone acts also within the cells in which it is found has not yet been decided.

To these facts have been added recently a number of quantitative data by Kuehn and Plagge (1936). The presence of an *A*-testis in an *a*-pupa for only 24 hr. suffices to produce the effect. One grafted ovary produces less of the hormone than one testis in 24 hr.; two ovaries produce more. A single egg tube, which is dissolved after transplantation, produces more hormone than a whole intact ovary, *viz.*, about the same amount as a day's production of a testis. (This is proved to be actually bound to the presence of the *A*-gene.) A dissolved testis, however, does not produce the hormone. It seems therefore that the testis produces, and the ovary stores, the hormone. The same hormone occurs in many other species of Lepidoptera, as transplanted testes from many different species produce the *A*-effect.

Another method, invented by Beadle and Ephrussi (1935-1937), has led to results that fall in line with those already mentioned. (Part of their work has already been mentioned on page 166.) They transplant in *Drosophila* the imaginal disks of eyes of different genetic constitutions into the body of larvae of definite constitution and recover the transplant after it has finished development in the host. Three types of result are possible. Either the transplant is not influenced by the host; *i.e.*, its development is autonomous; or the transplant assumes the color of the host. In the latter case, the host must produce a hormone-like substance, acting upon the transplant. As a third alternative, the transplant may be intermediate in color, which would amount to an insufficient hormonal action of the host. The diagram (Fig. 34) shows the authors' results with a large number of eye-color mutants. The majority of eye colors show autonomous development. But vermilion and cinnabar are exceptions; they are influenced by the host. Vermilion implanted into Wild type or into all the color mutants marked on top of the diagram gives Wild-type eyes with a few exceptions: it gives vermilion in claret (*ca*), carmine (*cn*), peach (*p^p*), and ruby (*rb*) and an intermediate condition in carnation (*car*) and garnet (*g²*) hosts. Parallel are the results with cinnabar, as may be read from the diagram. A Wild-type disk transplanted into mutants always gives Wild-type pigmentation with the

exception of a transplant into a *ca*-host, which becomes claret. There is finally another case, in which the transplant changes the host: a cinnabar eye disk transplanted into a host that is simultaneously apricot and vermilion makes the host's eye

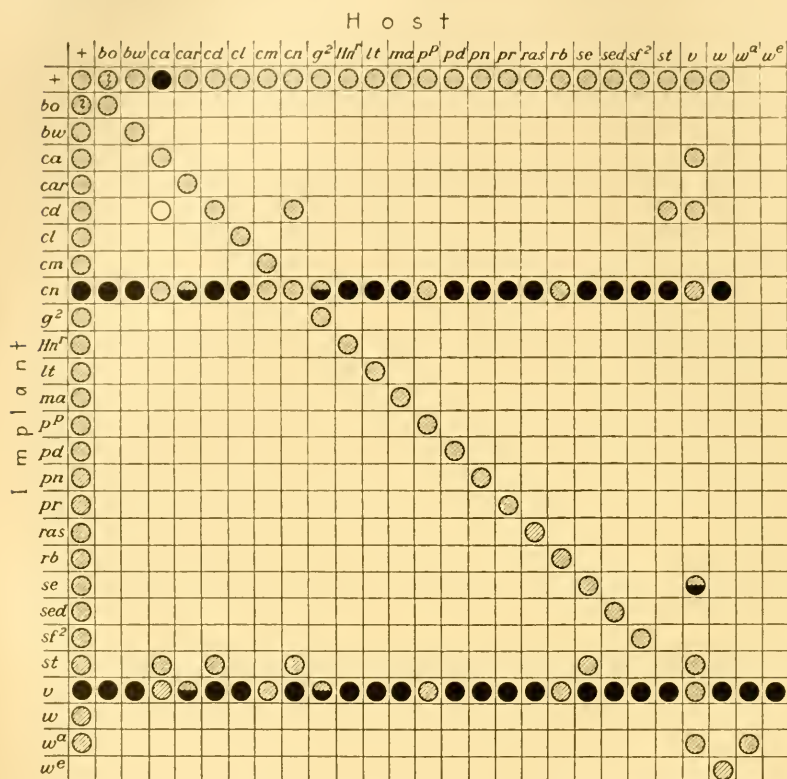


FIG. 34.—Diagrammatic representation of the first series of results of eye transplantation in *Drosophila*. Shaded circles, autonomous development of pigmentation of the implant; black, nonautonomous; half shaded, intermediate color. (From Beadle and Ephrussi, 1936, *Genet.* **21**.)

apricot. Thus, we have “hormonic” influences from host to implanted eye and from implanted eye to host's eye in certain cases. The first influence, however, did not originate in the gonad (as in the cases reported before) but in the fat body and Malpighian tubules.

From these results the authors conclude: Since the pigmentation of a genetically *v*-eye can be modified to *v*⁺ (Wild type) by

transplanting it to a Wild-type host, the host is supposed to furnish a substance (or hormone for its production) absent in a *v*-fly, a *v*⁺-substance. The same argumentation applies to a *cn*⁺-substance, which is proved to be different from the *v*⁺-substance, because a *v*-disk in a *cn*-host gives a Wild-type eye. In the Wild type, these substances are produced within the eye.

Recently Ephrussi, Clancy, and Beadle (1936) demonstrated the presence of this stuff in the lymph by injecting Wild-type lymph into apricot-vermilion pupae. The flies hatched with apricot eyes. It turned out that the stuff is produced in pupae 30 to 80 hr. old and acts upon pupae from before pupation up to 70 hr. after pupation.

The results regarding the claret character had shown that a genetically Wild-type eye could not become Wild type in a claret host; there must also be a *ca*⁺ substance, necessary for Wild type, which, however, is not formed in the eye itself. But as a *ca*-type eye in a Wild host does not become Wild type, there must also be something in the *ca*-effect within the eye that prevents Wild-type pigmentation. These three substances must, however, be closely related because the absence of one usually entails the absence of all. From these and other facts the authors conclude that the three substances are successive products of a chain reaction: $ca^+ \rightarrow v^+ \rightarrow cn^+$. The different mutant genes then produce either an interruption of this chain at some point or a retardation of its rate. In this way—which links these facts with our former discussions on rate—the details of all experiments may be explained. (See, however, footnote, p. 167.)

Recently (1937), Medvedev has used the Ephrussi-Beadle method for transplanting wing disks of mature larvae belonging to Wild type, yellow, ebony, and black into different hosts in different combinations. The result was always autonomous development, which means a negative result from the standpoint of this chapter.

At this point also an example from the plant kingdom may be inserted. Anderson and de Winton (1935) in studying the manifold action of some genes in *Primula* found that the genes *Ch* increase in the flower sepal and petal lobing; the gene *t* inhibits it; and both have an inhibiting effect upon peduncle elongation, though at opposite ends of the peduncle. They think

that this points to a difference in distribution of some regulatory substance, possibly a growth hormone. There is also a third gene *n* which probably acts upon the production of the same stuff.

In this chapter, we ought to mention also those cases where actual and known hormones are controlled by genic action. [We have discussed (page 77) the facts of inheritance of the number of molts in insects, controlled by a series of allelomorphic genes. In these cases, however, we need not assume that the genes in question lead to a production of hormones but only that they are connected with the time of release of a hormone. For this reason, the case was reported in the chapter on rates.]

There is, for example, the case of the dwarf gene in mice as analyzed by Smith and McDowell (1930). It was shown that this gene works by controlling the production of a growth hormone in the pituitary gland, the insufficiency of which leads to dwarfism and other abnormalities. Another probably more complicated case taken from the sphere of sex hormones is the much discussed case of the hen-feathered Bantam cocks. Hen-feathering is controlled by a dominant gene (perhaps two), as found by Morgan (1919) and Punnett and Bailey (1921). Castrated cocks become normally cock-feathered, and transplantation of any testis produces a return to hen-feathering. In normal fowl, the male type of plumage is the genetic type, and the female type is caused by the female sex hormone. According to Callow and Parkes (quoted from Haldane, 1935), the Bantam feathers respond with female type to a very low concentration of female hormone. As there is some female hormone also in normal testis secretion, the gene responsible for hen-feathering produces a low threshold of response to the female hormone. If these results are as significant as they appear, the gene in question actually does not control the production of the hormone, but a condition in the feather follicles, setting a threshold to hormone action.

It will probably be found that the production of hormone-like substances, *i.e.*, diffusion and vascular hormones, plays a much more important part in development than is known at present. We expect that such processes will be found wherever an organ differentiates in some respects as a unit. We know already some cases from which such a situation may be inferred. There is the case of the insect gonad, as analyzed in the intersexuality

experiments, *i.e.*, in a case where the normal genic action has been replaced by another one. Goldschmidt (1931c) studied the details of the transformation of a testis into an ovary, and vice versa. He found that the facts were not in favor of the assumption that the determining processes went on in the individual cells. He made it probable that the balance of the sex genes in this case either stimulated the sheath of the ovary to produce a hormone acting upon the whole gonad in transforming it into a testis; or, on the contrary, stimulated a group of cells in the attachment point of the vas deferens to the testicular compartments to produce a hormone, transforming the testis into an ovary.

From the study of intersexuality in *Lymantria*, many more cases may be derived. It is frequently found that an organ that has been developed first male and ought to become female later, or vice versa, after the turning point continues with its male differentiation, when that has once started, if no female homologous part exists into which it could be transformed. For example, in male intersexuality the valvae and penis of the genital armature may fully differentiate after the turning point; whereas the uncus is transformed into its female homologue, the labiae. From this we may conclude that at a certain stage of development the whole *Anlage* is determined by a hormone-like substance, produced by genic action; furthermore, that the action of this hormone has the maximum effect after a definite time of activity, just as in Kuehn's experiments (page 185) 24 hr. presence of hormone producer sufficed for full effect. It might be mentioned incidentally that here also is found the explanation for the special type of intersexes with both ovaries and testes produced in *Drosophila* by Lebedeff (1934). A similar conclusion may be derived from recent experimental work by Bytinsky-Salz (1933) and Bodenstein (1936). Salz found that certain species hybrids of *Lepidoptera* are unable to develop beyond a certain stage. The same organ transplanted to a pure species will be induced to behave like the host's organs. This looks like a kind of hormonal control of differentiation.

From the standpoint of experimental embryology, the facts just mentioned would be called an induction, and the application of the hormone concept is not absolutely necessary though rather probable, if cases like the gonad transformation are studied.

The specific structure of the testis, for example, makes an induction by simple contact rather improbable. After all, the differences between induction by diffusion and by hormones are found to disappear the more we learn about induction. Two sets of facts demonstrate this. Greenwood and Blyth (1935) showed that the sex hormone in quantities below a certain threshold is not distributed by the blood stream but diffuses only from cell to cell; the same substance is then once inductor by diffusion and again a real hormone. Another example relates to the other end of the series: Goldschmidt (1921a) found that in intersexual males of *Lymantria*, frequently duplications and triplication of parts of the male genital armature (the valvae) appeared. He concluded that the cause must be the increased breadth of the region of formation of these organs caused by the larger size of the intersexual abdomen. Recent work by Holtfreter (1936) shows that this explanation was right and why. This author showed that a stretching of the amphibian organizer resulted in multiple inductions. We concluded from the facts mentioned above that an induction of the hormonal type must be present in these parts of the genital armature. Here we have another proof, which in addition links the facts with the typical cases of embryonic induction.

3. Diffusion of Growth- or Similar Substances.—One of the most frequent actions of the mutant gene is the production of insufficient quantities (as compared with the normal gene) of substances needed for normal differentiation. Lacking detailed information, we might generally call them growth substances. We have met them before in cases where possibly processes within the individual cells were involved, *e.g.*, the bristle-forming materials in Plunkett's study (1926). A case where we can hardly escape an interpretation in terms of production of such substances, or their reciprocals, lytic substances, destroying previous growth, was the scalloping effect of the vestigial series, and the interpretation was already given in this sense. Here there can be no doubt that the mutant development is either short in some substance necessary for normal growth and differentiation; furthermore, that this deficiency may be of graded type and becoming effective at different times of development in different alleles or compounds; furthermore, that the insufficient quantity in question spreads across the wing from its base and reaches

the tip last; or that the diffusing substance is a lytic substance which is first accumulated in a quantity above the threshold of action in the wing tip with all the other graded consequences. The action of many other genes is of a similar type; the truncate wing and the miniature wing in *Drosophila* are examples in which other substances are involved, in the former case acting only upon mesoderm differentiation; in the miniature case, only upon growth after differentiation. This type of growth substances, in insufficiency and in hyperproduction as well as eventual lytic substance, might be responsible for a large majority of developmental processes in mutants, especially wherever linear growth or reduction is involved. They might also be responsible for all processes of differential growth; but here, of course, the pattern factor will come into play, perhaps in the form of different resistance to the diffusion of the substance in different directions of space. This part of the problem will be treated in a later chapter. It must be emphasized that in all these cases the unity upon which the mutant gene acts is a complicated system. The unit affected might be the whole organism (size and proportions) or a whole organ (an imaginal disk, a wing) or a definite part of an organ (the wing veins as a whole or one definite vein). Within these units, therefore, no mosaic formations are possible except when the last stages of development are involved (see miniature wing, Demerec, page 176). Moreover, different processes of this type, conditioned by different mutant genes, controlling the production of different substances, might be combined in the same individual without interfering much, with each other. For example, Goldschmidt (1937) showed that the large broad wing of the mutant expanded in *Drosophila* is determined even in the stage of the imaginal disk. A combination of the mutant genes expanded, dumpy, cut can produce a wing that is short-dumpy, broad and cut, in addition, because three substances are involved, produced at different times and acting upon different tissues, *viz.*, upon the general growth and upon epithelial and mesodermal differentiation (for data see Csik, 1933; Goldschmidt, 1937). If the same reactions with the same end product were involved, a compromise result, *e.g.*, intermediate, would be encountered. This, of course, is the case with compounds of multiple allelomorphs; but it might also be the case with different genes, *e.g.*, different genes for scalloping,

like beaded and beadex.¹ This problem has already been discussed in the chapter on interaction of the genes (page 161).

Of a different type but very important in connection with the problems of this and the last chapter is the work of Haemmerling (1934) on *Acetabularia* (See also page 179). This alga has the form of an umbrella with a long stem growing from a rootlike base. The umbrella-like spread is formed after a series of wreaths of hairs have been formed at the distal end of the stem and have disappeared. The umbrella itself consists of a number of individual radial chambers, in which the gametes will be formed later. This whole plant is only a single cell with a large nucleus situated at the base of the stem in the rhizoid. By cutting the stem, a nucleated part containing the rhizoid and an anucleated one ending in the umbrella, or "hat," will be obtained. The anucleated fragment will live a very long time but is finally doomed. Such a nucleated segment easily regenerates the lost parts. But an anucleated fragment may also regenerate the hat at the anterior as well as at the posterior cut end. It was then shown that this regeneration of anucleated fragments takes place more readily at the anterior end and that its success depends upon the presence of a substance that is used up during regeneration and shows a gradient of concentration, increasing toward the end of the stem. The same piece will also regenerate a rhizoid, and the stuffs responsible for this show the opposite gradient with a maximum concentration toward the base of the stem. The influence of the nucleus could then be tested in the following type of experiment. A piece with a nucleus was allowed to begin regeneration, and after it had been started the nucleus was removed. The piece now left had complete power of regeneration though derived from the part of the stem that otherwise would not form a hat. The nucleus then had produced the formative stuffs which spread along the stem. Such experiments show the nuclear origin of the formative stuffs but do not prove that it is the genic material within the nucleus that is involved here. This problem was attacked by using a second species (1. *A. mediterranea*, 2. *A. Wettsteinii*), differing from the first mainly by the number and shape of the chambers constituting the hat, the color, and a number of other characters. It was possible to transplant anucleated fragments of one species to

¹ Unpublished work.

nucleated ones of the other in both directions. In this case, the nucleated part controlled the differentiation: a mediterranea stem upon a nucleated *Wettsteinii* rhizoid forms a typical *Wettsteinii* umbrella. This shows that actually the genes within the nucleus control the production of a specific formative stuff (not unspecific, as in the hormonal type) which diffuses through the cytoplasm to the place of its form-controlling action.

It might be added finally that Gregory and his collaborators (1933-1936) have tried to trace the actual product of genic action responsible for hereditary size. As reported before (see page 54), hereditary size differences in mammals and birds (Castle and Gregory; Gregory *et al.*) as well as in insects (Goldschmidt) are based upon a different rate of cell division from the very start of development. According to a number of physiological investigations (Hammett, 1931), the concentration of glutathione in the body is somehow correlated with cell proliferation. Gregory therefore tested the glutathione content of embryos of large and small breeds of rabbits and of fowl and found them proportional to the adult size of the race. As it is believed that a high concentration of disulfides favors protein synthesis, the size genes might act via such intermediate steps.

4. The Determination Stream.—There is one series of facts that allows the forging of another interesting link between genetics and experimental embryology. When Goldschmidt (1920*b*) first developed his theory of gene action, he considered certain cases of pigment patterns in *Lepidoptera* with which he was familiar. There were especially cases of melanism which he had analyzed genetically, and which showed that the amount of pigment production, and also the arrangement of this pigment, was dependent upon a number of Mendelian genes. In some cases, it seemed that pigmentation started from one point (the wing base) and spread from there in different genic combinations across the wing in a definite path. In others, there seemed to be a number of predetermined centers at definite points from which this flow took place. Therefore the terms *outlet of pigment* and *pigment stream* were used, a movement not of pigment, but of pigment-determining substance being meant.

Later, another remarkable case was studied which led to a more definite statement (Goldschmidt, 1923*b*). Intersexual

males of *Lymantria dispar* are genetic males which have developed up to a certain time as males but, from a certain point on, have become female. Higher degree of intersexuality means earlier

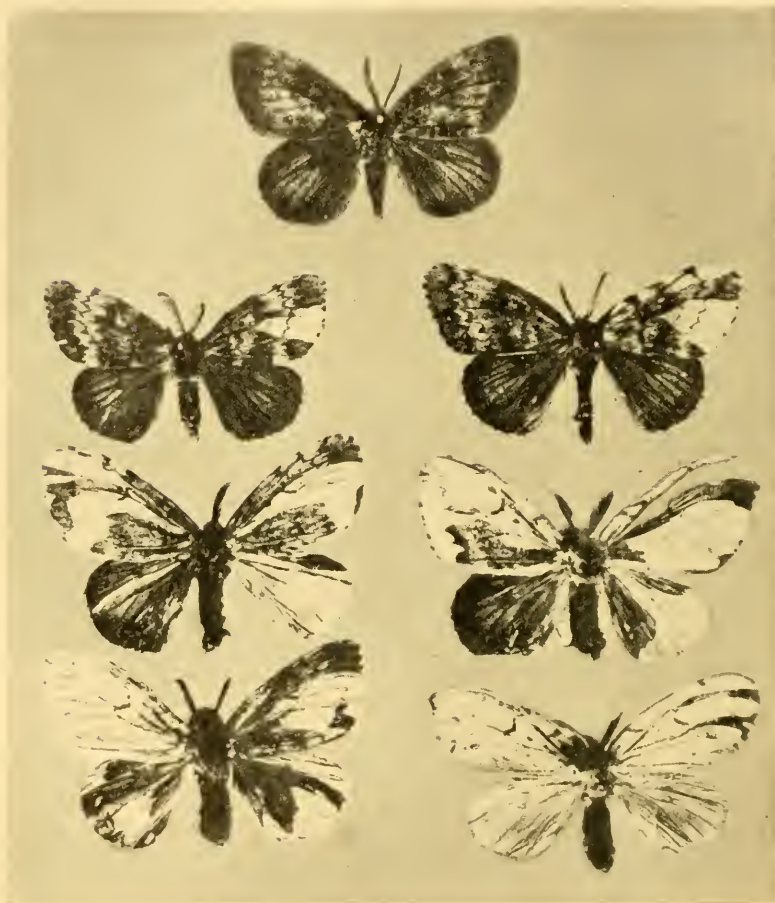


FIG. 35.—Series of intersexual males of *Lymantria dispar*.

turning point.¹ In this case, the wings exhibit a characteristic behavior (Fig. 35). In the very first stages of intersexuality, only one wing may show a small patch of female color and scale structure. (The problem of symmetry involved here will be

¹ In a series of recent papers Baltzer and Kosminsky have attacked the concept of a turning point at different times. A paper in press by the author disposes of their arguments in detail.

studied in a later chapter.) With increasing intersexuality, these patches increase on both wings without being symmetrical and finally cover a whole wing. If we look at such a series of wings of intersexual males of increasing femaleness, we are struck by the fact that the arrangement of the dark male and white female parts, irregular as it is, is of such a type that one might describe it in terms of a stream of pigment flowing from the wing base over the wing along the veins, covering the surface in an irregular way, leaving islands in between until the stream is stopped when all available pigment has flowed out (more in lower, less in higher intersexuality). Obviously, the quantity of "pigment" is a definite one for each stage of intersexuality and available simultaneously to all four wings, to which it is distributed by chance. An exact study of numerous individuals (Minami, 1925) bears out the general correctness of this picture.

Now, within dark male areas the form and arrangement of the scales is of the male type; and within the light areas, of the female type. The substance that has flowed across the wing therefore determines color, shape, and arrangement of scales of male type. As the amount of this substance is proportional to the degree of intersexuality, and as the degree of intersexuality is proportional to the time of occurrence of the turning point, it follows that the simplest picture that we can make of the process is the following. The differentiation of the male-type wing scales, in all their features, is controlled by a determining stuff, which enters the wing *Anlage* at its base and slowly flows across the wing, the channels being determined by the actual structure of the wing at this time. If the male is intersexual, this flow ceases at a definite time which is controlled by the degree of intersexuality; and the result is that all parts of the wing that have not yet been reached by the flow will develop as female parts. (The details may be conceived in different ways; the problem, however, belongs to the problems of sex differentiation). From this it follows that the visible patterns of male color and structure in a series of male intersexes indicate the progress and type of flow of an underlying determining substance. Adopting a conception introduced by Spemann, we call it the *determination stream* which thus is made actually visible; and inasmuch as the link with the specific genic combinations that produce intersexuality is known, we see that genes actually controlling color and struc-

ture of a wing may act by controlling a determination stream of definite quantity, speed of progress, pattern of flow, and action upon different processes of morphogenesis and chemism. It is surprising that these points of primary importance for the problem of gene action have never impressed other workers (with the exception of J. S. Huxley).

There is another point of greatest interest in connection with the same work. If a male *Lymantria dispar* becomes intersexual, the female wing color and wing structure appears upon the male wing, as just described. If, vice versa, the female becomes intersexual, the male wing color appears upon the female wing at once, all over the wing. It is known that the pattern of wing color is determined in a sensitive period before pupation, and we have seen how in the male the determination stream flows across the wing. The different behavior of the intersexual female must then mean that the time relations in regard to the flow of the stream across the wing are different in the female; even the latest turning point could leave still enough time for the determining process for the male color (and structure) to spread over the entire wing. (Actually, all time elements of growth and differentiation are different in both sexes, as analyzed in detail in Goldschmidt 1933.)

Giersberg (1929) has described and pictured a number of intersexes in different Lepidoptera which in part demonstrate beautifully the conception of the determination stream across the wing, an interpretation that he also accepts.

In recent years, Henke and Kuehn have applied the same conception to the interpretation of their experiments in shifting the wing pattern in Lepidoptera. The pattern aspect of the problem will be discussed in a later chapter. Here we consider only their proofs for gene action by controlling a stream of a determining stuff. We refrain from reporting Henke's first experiments on Saturniid moths, because no genetic work is available there, and report only the work on the flour moth *Ephestia kuehniella* where genetic, phenocopic, and experimental evidence are available.

Since the work of Sueffert (1925, 1927, 1929b), Schwanwitsch (1928-1929), and Kuehn (1926), it has been known that the complicated pattern upon the wing of Lepidoptera is the result of different arrangements of a number of always present constituent

parts or fields. One such characteristic field (see Fig. 36) is the symmetry field in the center of the wing, limited on each side by a system of bands. Its unity is proved by the fact that it acts as a whole when changed in phenocopic experiments and that it is affected as a whole by mutant genes. Definite temperature treatments may broaden this field if applied at a sensitive period or else narrow it. The same action is produced by a mutant gene *Sy*, which constricts this field. To find out how the size of this field is controlled, Kuehn and Henke (1936) (see also Kuehn and Engelhardt, 1933) destroyed definite parts of the

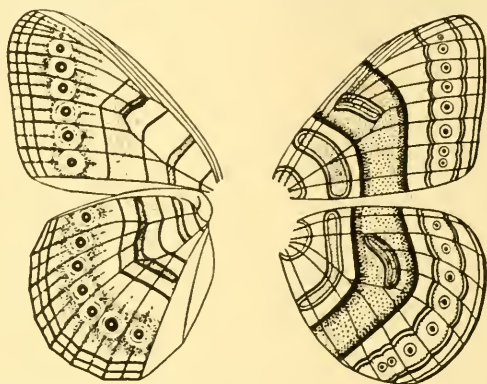


FIG. 36.—Diagrammatic representation of the elements of the pattern in nymphalids. Interpretation: left, by Schwanwitsch; right, by Suefert. (From Henke, 1935, *Verh. deutsch. Zool. Ges.*, Fig. 15.)

developing wing at different times and watched the effect with the following result: If the wound is made at the proper time (early pupa), the bands limiting the symmetry field are pushed around the wound in a definite way, which is well illustrated in Fig. 37. The resulting pattern is such as would be caused if a determination stream proceeded from the anterior and posterior margin of the wing in a broad front toward the center and if the edge of this stream, wherever it comes to a standstill, determined the position of the bands limiting the symmetry field. A comparison of Fig. 37 with the diagram (Fig. 38) beautifully illustrates the actuality of this conception. It is clear that earlier operations will produce this edge effect nearer to the wing margin and later ones toward the center and that still later ones might only affect the contour of the bands which become transverse after the two streams have united (see Fig. 37). Here, then, the embryological

experimentation demonstrates exactly the same thing as was derived by Goldschmidt from genetic experimentation.

Furthermore, in this case, a number of facts may be coordinated.

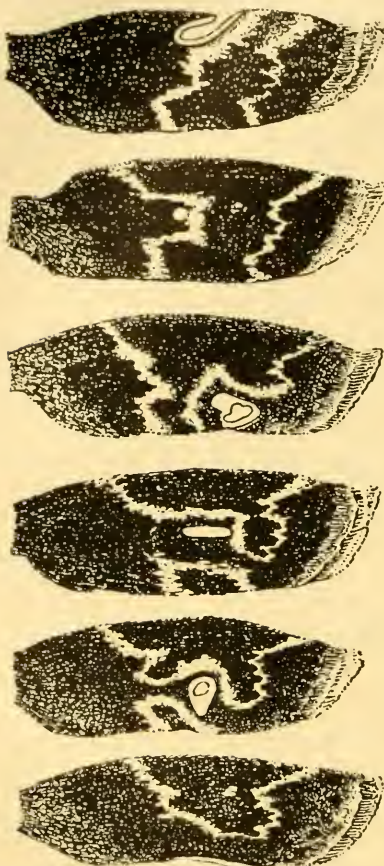


FIG. 37.—Right pupal wings of flour moths, black race, operated in pupae (0 to 24 hr. age). (From Kuehn and Henke, 1936, *Abh. Ges. Wiss. Goettingen*, 15, Fig. 96.)

1. The symmetry field may be enlarged and narrowed by temperature shocks at definite and different sensitive periods (see Fig. 7, page 21).

2. The same effect may be produced by a mutant gene.

3. The shifting effect upon the bands by destruction of wing tissue can be obtained best at the time of the sensitive period for narrowing the symmetry field (48- to 60-hr. pupa). Heat, as well as the gene *Sy*, acts by affecting quantitatively the course of the determination stream. This course may be directed by controlling the quantity of the determining substance, the time of its flow, or the limits that may prevent further expansion (which Goldschmidt had called the *conditions of the system*). Kuehn and Henke speak of *force of expansion* and *force of resistance* (of and to the stream) which is the same as quantity or time of flow of the determining stuff and the conditions of the system in Goldschmidt's old

terminology. It might finally be added that Kuehn and Engelhardt (1936) performed the same type of experiments upon the currant moth, *Abraxas grossulariata*, with practically the same results aside from minor differences in detail.

The idea of gene action by means of a determination stream has also occasionally been employed by *Drosophila* workers. Thus Plunkett (1926) found that the bristle-destroying action of the

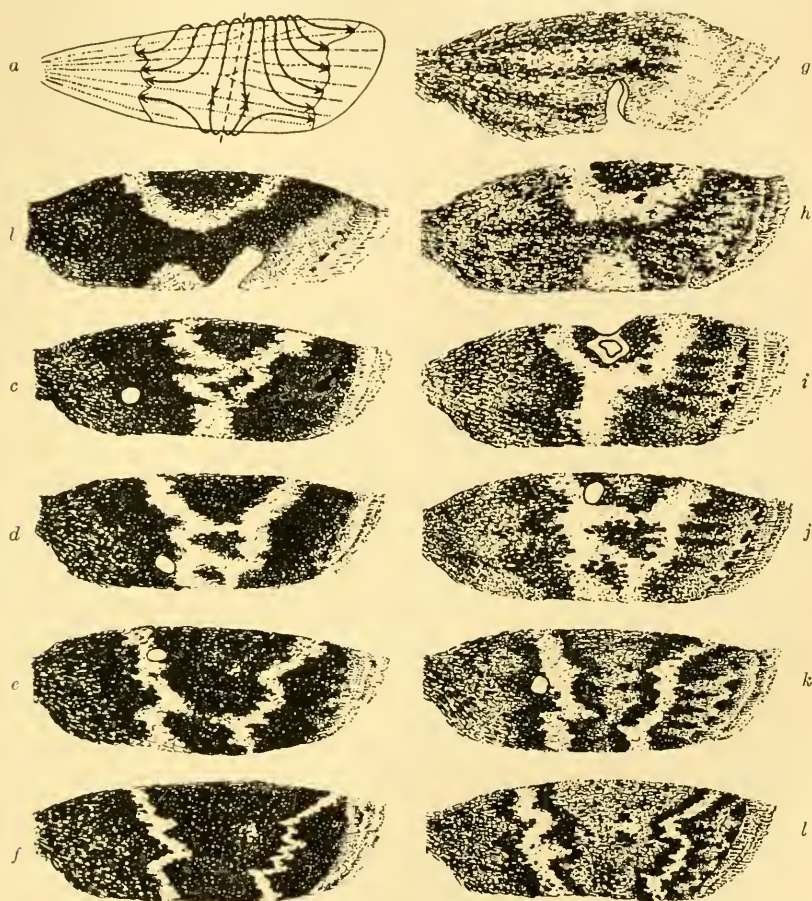


FIG. 38.—Flour moth. *a*, diagram of the spread of the determination stream; *b-l*, individual right pupal wings; *b-f*, black race; *g-l*, wild race; *f, l*, controls. Age at operation *g* below 6^h, *b* below 24^h *c-e*, *h-k* 24-72^h. (From Kuehn and Henke, 1936, *Abh. Ges. Wiss. Goettingen* **15**, Fig. 97.)

achaete gene spread from the center of its action (a definite bristle) equally in all directions. As he assumes that the decisive agent is a catalyst, he thinks that this diffuses from its point of origin in all directions, a process, then, that we might describe

also as a determination stream. Other cases of the same type will be mentioned in the next chapter (see page 229).

In plants, we have already mentioned the determinative processes in *Acetabularia* (Haemmerling) dependent upon the flow of a substance which may be called a determination stream. Such a process in relation to definite genes would probably be found if a genetic analysis of flower abnormalities were combined with embryological experimentation. A not very clear hint that such is the case may be derived from some remarks of Zimmermann (1934) concerning hereditary traits in *Anemone*. Also, mutations of the type of laciniate leaves might permit an analysis in that direction.

9. THE PROBLEM OF PATTERN

In the preceding chapter, we were confronted with the problem of pattern, the most important problem for both the geneticist and the embryologist. Development is, of course, the orderly production of pattern, and therefore, after all, genes must control pattern. It is a formation of pattern when the axial organs in an amphibian are determined; it is also formation of pattern when the digits of a hand are laid down, as well as when two blastomeres of different potency are separated. Most of our knowledge of pattern formation comes from experimental embryology, which is the science of analysis of pattern formation. We must now try to find out whether genetics has furnished material that permits an attack upon the problem of pattern in terms of gene action. Before doing this, however, we ought to have definite notions regarding this problem, as it emerges from the facts of experimental embryology, according to our ways of interpreting these facts.

A. PATTERN IN DEVELOPMENT

Development, if considered apart from the component cells, consists of a series of steps restricting the potencies of different areas, which are thus consecutively subdivided into smaller and smaller areas of more and more specialized determination. For each part or organ or structure, then, sooner or later comes a time whence its future is finally determined¹ or, in the language

¹ Harrison (1937) wants the term *final determination* eliminated because each determination is not final. But as it is final in normal development,

of Driesch, whence its prospective potency is identical with its prospective fate. The processes that lead to this type of pattern formation are usually conceived as being of two types, self-differentiation and dependent, or inductive, differentiation. But it may be regarded as certain now that these two types of developmental activity are, in fact, only two phases of the same process. If we try to describe an inductive process in a most general way, it would be one that leads to pattern-like restriction of potencies in an area outside the area containing the inductive agent. Induction of pattern by a process or product of a process within the area to be subdivided would also be induction (see page 202). It would then be an inductive action if a hormone were sent to the area of induction or if a substance formed in the inductor were to diffuse into the area to be induced or if a contact between two areas, if established, were to produce an unknown physical effect, followed by pattern formation.¹

The best known inductive agency is the organizing center of amphibians. We know that its active substance, at least for the general inductive effect, is a relatively simple chemical compound (though unanimity is not yet established regarding its actual nature); therefore the inducing action must be conceived as diffusion of this substance into another area. This process, then, would be comparable to the determination stream already mentioned, though not completely. Furthermore, we know that there is a regional differentiation within the inductor area, which has different inductive effects, *e.g.*, a part that may induce only head pattern. This shows, then, the presence of a pattern within the inductive area, whatever it is. An inductor, then, is something rather general (not very specific); something that may show a certain diversity within this generalized nature; something that is moved to adjacent areas; something that makes the area upon which it acts diversify, form a pattern, the details of which depend upon the constitution of the inductor substance and upon the condition of the area to be induced. Finally, the first set of inductors may be followed by a second or secondary one within

controlled by genes, and also final in the average type of experimentation, we feel entitled to use this conception.

¹ The general literature on experimental embryology will not be quoted in this section, except when special examples are used in connection with the topic of this book.

the newly diversified areas, and so on. Induction, then, is a process that provokes pattern formation but does not explain it.

Self-differentiation means that for the area in question pattern formation has been ended. It will not be subdivided any more. If it occurs late in development, it will be the final outcome and the end of the series of inductive processes. If it begins early in development, it means that pattern formation has occurred early. In these cases, it might have been preceded by induction, but it might also be that induction had taken place so early in development, even within the egg, that it would actually coincide with pattern formation. This would mean that the inductor is produced within the area upon which it acts as an evocator of pattern. (Example: the induction of pattern in the egg as a consequence of the bursting of the germinal vesicle.) Induction, then, is one of the methods of initiating pattern formation. It therefore does not explain pattern formation. This is an important point, because the beauty of the experiments with the "organizer" has led to a general belief that here the causative principle of development was discovered. In fact, only an evocator (Waddington) was found which in certain stages and in certain cases acts like a fuse to set in motion the actual pattern-forming process.

The following processes, then, have been found by experimental embryology to combine in development, according to our notion:

1. The ability of different embryonic areas to be broken up into subareas according to a definite pattern; a process to be followed later by a similar subdivision of these subareas.

2. The possibility that these pattern formations may be started at different times in development of different species, either in the whole embryo or within different parts of the same embryo. Late patterning means equipotential development; early patterning, mosaic development.

3. The breaking up of areas (or embryonic fields) into subareas finally leads to a point where each area is so restricted in potency that only one type of further differentiation is, as a rule, possible. The area is determined.

4. The breaking up of one area into subareas, the process of patterning occurs in orderly fashion both as to time and as to localization in normal development. Regardless of all other

control of development by heredity, it is first bound to control this sequence of patterning.

5. The process of pattern formation may be evocated by evocator substances diffusing into the area from an adjacent area or center (organizer type) or by substances diffusing from larger or smaller, already formed areas in definite directions. In the latter case, it cannot be decided whether an evocator is actually present or the observed process of diffusion, *e.g.*, sea-urchin egg, amounts to separation of the pattern-forming substances. Something, however, must initiate this process and might be called an evocator, produced within the area upon which it acts, but this need not necessarily be a substance; it might also be the pH situation or an electric charge, etc.

6. The type of pattern formed depends upon the nature of the evocator (example: head and tail organizer), the nature of the area (example: newt evocator acting upon frog-mouth area), and probably also upon the conditions of the whole developing system (example: different success in transplant and explant.) The problem of regulation has been barred from this general review. This is how we conceive of the general picture of development as derived from modern work. (The facts of experimental embryology are assumed to be known to the reader.) The action of the hereditary material, then, has to be linked with these primary processes.

Before we begin to study the facts, some information should be presented regarding the decisive process of patterning. Genes or mutant genes that control development ought to be responsible for the initiation of such a process at definite times and places by some type of evocation. What follows, the subdivision of the field, may be a wholly automatic, *i.e.*, physicochemical, consequence of the situation created. The actual process of pattern formation must therefore be of a rather generalized type; as a matter of fact, it may be any type of process that leads to a redistribution of substances within a given system (or eventually of physical conditions like viscosity, charge, dispersion).

A considerable number of investigators have tried to formulate definite ideas of this process. One point of view, couched in physiological language, is Child's theory of gradients which, applied to our problem, would mean that a gradient of intensity of metabolic processes produces different conditions in a set

direction, which will be followed by morphogenetic differences. The evocator then would determine the center of a metabolic gradient, and the different levels of the gradient would determine the different parts of a pattern.

Another viewpoint of a more general type is Lillie's theory of segregation (1929). According to Lillie, *embryonic segregation* is the process of origin of the diverse specific potencies that appear in the organism in the course of the life history, which express themselves later in tissues of specific structure and function. The criterion of segregation is self-differentiation. Segregation proceeds from the more general to the more special until further segregation is closed. Thus far, this conception is practically identical with all other similar conceptions. Lillie, however, postulates that this segregation is dichotomous. It is not clear whether he means only a dichotomy into parts with restricted and nonrestricted determination or thinks that simultaneously only two areas may be formed, not a complete pattern of areas with different restricted potencies. This dichotomy may coincide with cell divisions in the case of cell lineage, and it may also cover multicellular areas. Only a comparatively small number of such segregations occur in ontogeny. Inductive processes are those which cause segregation to take place. Segregation, however, does not separate organ-forming stuffs but possibly only different proteins (which is the same, Author). This theory, though couched in somewhat different terms, is after all not very different from others here reported.

Another more generalized point of view is the theory of embryonic fields in the slightly differing types worked out by Gurwitsch, Weiss, and Guyénot (see Weiss's review, 1935). They compare the area that is to be subdivided to a field of force (without making special physical assumptions) that is being subdivided by the evocation of new conditions of equilibrium. (This is only a very generalized statement of these views.) Another view has been developed by Goldschmidt (1927c). He uses as an inorganic model the formation of Liesegang rings in a colloidal solution, evoked by the infusion of a definite substance. With a generalized expression he calls such a diversification within a unit, produced by a chemical or physical evocation, a process of stratification; this might work via all known chemical or physical processes such as change of charge,

processes of diffusion, separation, changes of viscosity, adsorption, chemical equilibrium, sedimentation, etc. In Liesegang-ring formation, the nature of the solution, the nature of the evocator substance, and the whole system (arrangement and texture of filter paper, etc.) will determine what the pattern of the rings will be. In development also, the nature of the evocator and of the area to be patterned, together with the conditions of the whole system, will decide the pattern within this area. Many different processes of diversification within a given physico-chemical system after the model of Liesegang rings are imaginable. All have in common that an act of evocation (in the model, putting a drop of a certain chemical to a certain point) automatically produces a definite equilibrium arrangement of present or newly formed different substances in the form of a pattern, a process designated by the general term *stratification*. (A point of view practically identical with ours has recently been derived by von Ubisch (1936) from his work on sea urchins and also by Lindahl (1936), who actually established some chemical patterns.)

Finally, Harrison's views (1937) may be mentioned, though he has thus far pointed out only the general direction of his deliberations. He thinks that change in the spacing of the atomic lattice within the molecules of living matter may turn out to be relevant for cytoplasmic differentiation.

The important thing that is at the basis of these formulations, and that characterizes the developmental process which ought to be linked directly with the action of the genes, is the automatic physicochemical process of pattern (= equilibrium) formation, given evocation at definite time and place and the conditions of the whole system and its parts.

B. GENES CONTROLLING DEVELOPMENTAL PROCESSES

A discussion of the problems of development with the ultimate purpose of understanding the action of the genes presupposes that the decisive steps in development are controlled by gene activity. Most biologists who have discussed the problem of whether the promorphological features of the egg before fertilization—early formation of pattern (organ-forming areas)—or in early development are controlled by genes have come to the

conclusion that this is the case (Boveri, Wilson, Conklin, Morgan, Goldschmidt, etc.). Though it would be difficult to contradict such an assumption, the question ought to be answered whether or not facts are known supporting such a self-evident assumption. Actually, there are not many such facts. This is to be expected, as only rare cases are imaginable in which the action of mutant genes upon such early processes could be analyzed. But those which are known justify such a generalization. There is the work of Toyama (1909) and Tanaka (1924) on characters of silkworm eggs. These are different colors of yolk, already existing in the unfertilized egg, and colors of the serosa, a membrane formed by the blastoderm cells. These early embryonic characters are determined by mutant genes. (For an interpretation see the pigmentation hormone on page 184.) A more direct relation to the pattern problem is provided by the facts regarding right- and left-hand coiling in molluses. It has been known for a long time that this may be a modification in some cases and a hereditary trait in others. The genetic analysis of such cases by Boycott *et al.* (1930), Sturtevant (1923), and Crampton (1924) showed a Mendelian behavior with the addition that F_1 behaved like the mother, F_2 like F_1 in the classic case, and F_3 like F_2 . This means, as first shown by Toyama, that a character of the egg is involved that has already been determined before fertilization, so that the influence of the sperm will be felt only in the eggs of the next generation. The embryological work of Kofoed (1895) and Conklin (1903) had actually shown that the direction of coiling is already determined when segmentation begins; *i.e.*, it is laid down in a promorphological structure of the egg. Here, then, certainly, one of the primary processes of pattern formation is controlled by mutant genes. Another example of this type is furnished by Tanaka's work, already mentioned. Among the characters of early stages that were studied there was one type of pigmentation of the blastoderm which was inherited in the way just described (wrongly so-called maternal inheritance), which proves determination before fertilization. Blastoderm formation is a form of pattern formation of a special type in the insect egg, and the pigment thus serves as a marker of the separation (stratification) of one embryonic area controlled by mutant genes. A similar case has also been reported by Sexton and Pantin (1927) for larval lipochrome colors in *Gammarus*.

There are several cases involving this so-called *maternal inheritance*, in which it is difficult to form an idea of the type of prefertilization influence of genes upon cytoplasmic structure. In some of these cases, it is not even completely certain whether or not the interpretation is correct. Thus, Morgan (1912, 1915) claimed a prematuration effect to explain irregularities in the inheritance of the gene rudimentary; Lynch (1919) applied the idea to an explanation of sterility in rudimentary and fused (*Drosophila*); Redfield (1926) claimed maternal inheritance for a sex-linked lethal in *Drosophila* which acts only when the mother is homozygous for a second chromosome gene; Gabritschevsky and Bridges (1928) found a maternal effect upon the eggs of homozygous females for an enhancer gene of giant in *Drosophila*.

Rather remarkable are such cases of maternal inheritance in which the effect of genes acting upon the organization of the egg cytoplasm prior to fertilization becomes visible only in later developing parts of the body. Dobzhansky (1935) found such an effect in reciprocal crosses of two races of *Drosophila pseudoobscura*, controlling the size of testes. An autosomal gene acting on the egg plasm is responsible. In this same form, Dobzhansky and Sturtevant (1935) described a number of further hereditary characters with maternal inheritance, *viz.*, viability, sex ratio, rate of development. The latter characters may be understood more easily as controlled by a general plasmatic condition induced by genes. There is also a statement by Warren (1924) that egg size in *Drosophila* is controlled thus. It is more difficult, however, to understand the findings of Timofeeff (1935) that a gene controlling the pattern of bristles in the thorax of *D. funebris* (polychaeta gene) shows maternal inheritance. A predetermination of a pattern of thoracical epidermis in the cytoplasm of the egg is more than could be expected even in cases of development with very early determination (self-differentiation).

There are many facts showing that details of later stages of development are influenced by mutant genes. The whole body of work upon Mendelizing characters of larvae of insects (silkworm, *Lymantria dispar*, and *L. monacha* by Toyama, Tanaka, Goldschmidt, etc.) could be mentioned. There are also larval characters in *Drosophila* controlled by genes (Chubby, Dobzhansky and Duncan, 1933). In plants, all the endosperm and cotyledon characters belong in this category, also characters of the protonema in mosses; moreover, the influence of genes upon rate

of segmentation (Castle and Gregory) ought to be mentioned, and the whole series of lethals which act upon early development.

Nearly related are the cases in which mutant genes influence directly early pattern formation in vertebrates, though the exact type of influence is not always known. These are the cases of monstrosities in vertebrates which we have already reported (see page 46), some of which demonstrate a genic action at a very early time of development, probably upon the organizer directly (see Lehmann, page 50). To this category belong also all such lethal genes as are known to kill the embryo in very early stages, probably by upsetting primary pattern formation, *e.g.*, the cases analyzed in *Drosophila* by Redfield (1926).

Another group of most important facts has been derived from the study of a phenomenon called *homocosis*. We have described on page 36 the development of the mutant *aristapedia* in *Drosophila* in which the last segment of the antenna is transformed into a tarsus. We saw that this differentiation of a homologous organ takes place at the time of leg differentiation which occurs prior to the time of differentiation of the antenna. Here, then, a mutant gene changes an embryological process by shifting its initiation to a different point in time. There are similar cases in *Drosophila* which, however, are not so clear as this one. There are the mutations *bithorax* and *tetraptera* (see Astauroff, 1929) in which the metathorax assumes a number of characters of the mesothorax, including the formation of wings instead of halteres. There cannot be any doubt that the explanation will be of the same type as for *aristapedia*. There is also the mutant *proboscipedia* (Bridges and Dobzhansky, 1933). Here the mouth parts undergo a number of variable changes which bring their structure near to the type of biting organs of other insects. The modified lobes may show resemblance to the labrum, maxillary palpi, antennae, and tarsi, the homology of all these organs being apparent. Again, the same type of interpretation applies as in the case of *aristapedia*. These facts are of greatest importance in linking gene action with developmental processes. They point out that the mutant gene in question does not control a localized action of a special type. It controls a general, quantitative process which leads to a special result, because it shifts a process of pattern formation into a phase in which it ought not to be. To be more specific, at the

time when the pattern of the tarsus in the leg disks is laid down by a process of rhythmical subdivision of the distal end of the *Anlage*, something, an evocator, is present in the germ that diffuses into the *Anlagen* of the segmental appendages to produce this result. Disks in the proper stage of development will react to this induction by tarsus formation. Normally, the antennal disk is far behind in differentiation at this time and is not influenced by the evocator. The mutant gene, which speeds up antennal differentiation, however, makes the antennal disk mature simultaneously with the leg disks; and the evocator substance, which "orders" the formation of tarsus segments, therefore also acts in this disk. Here we have a case where a simple shift in the time element of gene action results automatically in a complicated morphogenetic change. Such facts show a system of genic action at work which we have discussed in a former chapter as the system of reaction velocities in tune. Here we may finally draw attention to the great evolutionary significance of such facts in connection with the problem of single large steps, the problem of the "hopeful monsters" as Goldschmidt (1933*d*) has called it, which is much more serious than this terminology would indicate.

C. GENES AND PATTERN

The facts just described justify the conclusion that the process of embryonic stratification is controlled by the action of the genes. To gain further insight we must, however, turn to more easily accessible forms of pattern, which may serve as models from which generalized conclusions upon all kinds of pattern may be drawn.

Different types of pattern are available for such studies. As the most elementary type may be considered the simple growth pattern, *i.e.*, the pattern-like typical differences in growth in the three dimensions which lead to the establishment of a definite form of all developmental units. Much work has been done in this line to establish the general laws of differential growth, to mention only D'Arcy Thompson (1916) and J. S. Huxley (1932). The insight that these authors gained has to be linked with specific genic action which might set in motion the pattern of differential growth.

It is only a short step from a growth pattern to a pattern of an area type, as the work on certain patterns in insects has shown. Long ago, Goldschmidt (1920*b, d*) pointed out that the insect wing and especially the wing of Lepidoptera might serve as a model because rather complicated patterns of form, structure, and color here are found in a more or less bidimensional arrangement, and because this pattern is accessible to genetical as well as embryological experimentation. The first steps in this direction were published in 1920*d*; more material was added later; and a comprehensive theoretical treatment was given in 1927*c*. Recently this problem has been attacked mainly by Henke, Kuehn, and their students, and the body of facts now available furnishes considerable information.

These two main types of pattern formation have some additional special aspects. There are patterns of primary importance for the progress of development, *e.g.*, the pattern that is laid down in the formation of an insect wing with the proper arrangement of veins, etc. But there are also secondary patterns which are superimposed upon the primary patterns late in development, *e.g.*, melanism, spread of dark pigment, upon an otherwise completely patterned wing. There is, moreover, the problem of symmetrical arrangement of the patterns on both sides of the body, a problem that might furnish decisive information upon the pattern problem in general. The following chapters will deal with these and other aspects of the pattern problem as related to gene action.

1. Pattern of Growth and Form.—If we refrain from a detailed discussion of differential or heterogonic growth (which is found in the book of Huxley, 1932), we may state in a few words the points that are essential from the standpoint of physiological genetics. Very different and specific forms and shapes in two or three dimensions may be produced if the process of growth in different directions occurs according to a definite rule, containing variables the values of which produce a definite result. Huxley found an exponential formula that accounts for all cases of differential growth and contains two decisive constants. The value of these constants determines the numerical system that the differential growth will follow in each case. Whatever the specific merits of this formula may be (see discussion by Hersh and Feldman, 1936), it furnishes, if considered in a general way,

a clue to the possibility of linking gene action with the production of growth patterns: any gene that controls quantitatively the rate of any one process, which is represented by the constants of the formula, automatically produces a definite result in terms of form. Form, then, would also be of the type of automatic pattern formation: something connected with growth produced at a definite time and place and in a definite quantity sets the pace for the working of differential growth by fixing the numerical value of the constants in the formula; it acts in this sense also as an evocator of pattern.

This important conclusion had already been derived by Goldschmidt (1920*b*) from D'Arcy Thompson's (1917) classic work on growth and form (including also the phylogenetic significance, which recently has been emphasized again by Huxley, 1932, and tested in an admirable way by Hersh, 1934*a*). Goldschmidt wrote:

Let us suppose that we succeeded in reducing all processes of morphological differentiation to simple physical and mathematical conditions, to surface tension and to all the geometrical consequences of differential growth, etc., the problem of heredity remains the same: to find why, at a given moment in given rhythm and localization, the specific chemical and physical situation is produced, the consequence of which may be stated as the mathematical law of development. . . . [Here follows a statement of the theory of rates of reactions in time.] . . . This quantitative conception makes it possible to refer extraordinary differences in the end result, *i.e.*, evolution within considerable limits, to very small causative processes. One may find in Thompson's brilliant book how the production of all forms of shells may be reduced to small changes in the values of the terms of the underlying equations for the actually found curves; and therefore how then a series of morphological differences may be shown to be produced by changes in differential growth within simple mathematical laws. Remembering our proof (in the work on intersexuality) that very specific differential growth may be started by the production of specific hormones [here in the sense of determining stuffs, evocators] at a definite time, one might realize the number of evolutionary processes which might be caused by small changes in the underlying genes followed automatically by numerous shifts in the interplay of properly timed coordinations.

The genetic facts that permit the derivation of such views are only beginning to be studied quantitatively. In earlier chapters, we have mentioned a number of facts that have to do with

determination of growth. Before analyzing differential growth, we may review shortly the pertinent genetic and other facts concerning growth in general. In animals, as well as in plants, the size of an organ (or the whole body) depends upon two processes, cell division and increase in cell size. Usually these follow each other in individual development; *i.e.*, at a certain time, cell division ceases, and growth of cells begins. There are many examples, one of them found in the butterfly wing where epidermal cell division ceases when the formation of scales with corresponding cell growth begins. In the *Drosophila* wing, we have seen that cell growth begins after the structure of the wing is completed. The same two processes are found in the development of a bird's feather or in the growth of a fruit. The most extreme case is found in such cell-constant animals as the nematodes (Goldschmidt, Martini), the Rotatoria (Martini), and the Acanthocephala (Van Cleave) in which a limited number of cells composes all organs, cells that might grow to an immense size without further division. Genetically, the two consecutive types of growth may be controlled by different genes. It is known that in *Drosophila* the wing-mutant Miniature prevents only the cell growth following a normal development during the phase of cell division and differentiation (Dobzhansky, 1929; Goldschmidt, 1935*c*, 1937). The wing mutant Expanded (large broadened wing), however, is produced by a different amount of growth in the period of cell division (Goldschmidt, 1937). It is possible to combine both genes in one individual, with the result that a broad wing is formed in the first phase which, however, does not grow in the second (Csik, 1934*a*). These facts show that the size produced by growth may be controlled by genes affecting at least these two processes of growth, maybe differentially. But differences in size may also be influenced by other genes acting on growth in general, irrespective of the two phases. It is therefore to be expected that in different cases different relations might be found. To mention some: Hough-taling (1935) has studied fruit size in tomatoes which, according to Lindstrom (1928), is controlled by a number of genes with different effect. He found that in the ovary of the large forms more cells are present and that, in addition, larger cells are found in the larger fruits; *i.e.*, both processes of growth are changed by mutant genes. The first, cell division, is ended about flowering

time and has then already produced size differences in the different stocks. Then growth of the individual cells begins and also lasts relatively longer in the larger races, thus producing larger cells. In this case, then, both phases of growth are determined together at an early stage (as opposed to the quoted case in *Drosophila*). A similar result was also derived by Sinnott, Houghtaling, and Blakeslee (1934) for polyploids and trisomics of *Datura*, where it is concluded that some genes control increase in cell size, others increase the rate of cell division. Somewhat different is the case of inherited size differences in *Lymantria dispar* (Goldschmidt, 1932*d*, 1933*a*). Here the growth by cell division starts with eggs of the same size in races of different genetic size, the differences of which are controlled by a number of genes. As is indicated by the growth curves of the larval stages, cell division is faster from the beginning in the larger races (with the addition of sexual differences between the large females and small males). This agrees with the findings of Castle and Gregory (1929) in rabbits of different hereditary size. But in *Lymantria* there is also an additional growth by increase in cell size, as it was proved that size of spermatocytes and of wing scales—two types of cells with considerable post-division growth—increases in proportion to inherited body size. But the same increase of size of these cells is also found in larger plus variants of a small race. The nonhereditary factors, then, act in the same direction upon cell size. This might mean—though not necessarily—that the second phase of growth is dependent upon actual size reached at time of pupation which in all cases will be followed by a definite percentage cell growth. These few examples show that growth of a body or organ may be determined by genic control of one primary process of rate of cell division, possibly by the production of growth hormones at definite times and in definite quantities; further, by control of the secondary process of increase in cell size (in plants known to be under auxin control); further, by control of the relative times of beginning and ending of both processes and also of their relative intensity. The integrated effect of such of these elements as may be present in the individual case is the measured linear growth.

Now to the problem of this chapter—the pattern of form by differential growth and its eventual explanation by a single or a

few genic actions, controlling one of the just-mentioned variables within the parts that grow at a differential rate from others, thus producing a pattern of form. We have already met with cases which might be described in this way, when we studied the production of hereditary abnormalities by changes in definite areas of early embryonic stages: the rumpless fowl, the mice with deformed tails, etc. Another example, which we mentioned there briefly, the creeper fowl, shows, however, that here a different type of production of form pattern is involved. According to Landauer and Dunn (1930) and Landauer (1931, 1934), the creeper fowl, a short-legged fowl, is the result of a dominant mutation which is practically lethal when homozygous. The limbs here were shown to be smaller even in the earliest stage of their visibility, and all their further growth occurs at the normal rate. The special pattern of Short-leggedness is then not produced by a change in the variables of growth of the limb but by a change acting only upon the early embryonic *Anlage* of the limb—a slowing up of differentiation in the early determination field of the limb. (But there is also a smaller effect upon growth in general.) The various bones are not equally affected. The more distal bones in the limbs which are determined later are more affected; the proximal ones, which have at least partly been determined before the retardation within the *Anlage* set in, are less affected. The fact that the longer bones are more affected indicates that tissues with the larger growth intensity are more affected by the retarding action in the *Anlage*. In agreement with this interpretation is the fact that the homozygous embryos which die at an earlier stage show a large retardation in growth during the first days of incubation, which most strongly affects those organs that are found at this time in their most active stage of growth. Landauer, therefore, concludes that a general retardation of growth in early stages, which become localized by the more ready response of parts in most active growth, is responsible for all phenomena. If this interpretation is correct, the case does not actually belong to the group of patterning by differential growth, because the pattern is produced by a change in a general rate process, which automatically affects more strongly such parts as are in active growth. Probably the same explanation applies also to the other cases of a similar type (reported on page 47ff.), according

to the view taken by Sinnott and Dunn (1935), who cite an additional case from their laboratory (kinked tail in mice, after Kamenoff (1934)).

But information is also available for animals that suggests that the genic control of differential growth is one of the means of pattern production by simple effects of genes upon one process with the consequence of an automatic patterning. Among the phenocopies that Goldschmidt (1929*a*, 1935*a*) produced in *Drosophila* by heat shocks was one that consisted of a change of the wing shape into a lancet form; all transitions from normal to lancet shape could be produced, apparently as a result of the establishment of a new differential growth in length and breadth of the wing in favor of length. In this case, only the second phase of growth, by enlargement of cells, has been involved, and mutants of this type are not yet known(?). But the simple quantitative increase of the heat effect in the series of types suggests a rather simple change of rate of something as the basis for the production of the different shape.

Another case, in which the genetic side is also known, is the case of the Bar eye in *Drosophila* according to Hersh (1928). It is known that the eye of *Drosophila* (and other Diptera) is—visibly or invisibly—subdivided into dorsal and ventral lobes. In the Bar-eye mutants, these lobes become clearly visible. Hersh found that the temperature effects upon the eye are different in both lobes, the ventral lobe decreasing at a faster rate with a rise in temperature. A statistical study of the data for different genetic compositions led to the conclusion that formation of facets (or destruction of facet-forming substance, Author) occurs according to Huxley's equation for heterogonic growth. As the ommatidia are differentiated in the optic disk primarily by an induction from the brain (see page 34), the growth pattern (ventral and dorsal lobe) may be the consequence of a gradient (determination-stream, Author) or of a primary inductive difference. However this may be, Hersh concludes that the genes of the Bar series produce their effects by altering the distribution of growth in the developing zygote. As he finds that Ultrabar larvae grow faster, it may be assumed that the facet-forming reaction will have a different time relation to the general curve of growth. "The manner of action of genes which affect the size of the eye, as determined by the number of ommatidia, would

seem to reduce itself to a question of the distribution of growth in the zygote." (It is of interest to note that exactly the same conclusion, though couched in somewhat different language, had been derived by Goldschmidt, 1927c from a general theoretical analysis of the case.)

In a later paper, Hersh (1934c) could specify these statements by calculations based on Driver's data, and this new statement gives exactly the type of information for which we are looking at this point of our discussion. The relative growth function, according to Huxley, is $y = bx^k$ which means that if y increases by a certain percentage, the variable x increases by another certain fixed percentage. The ratio of the percentage increases of x and y is the value of k , the coefficient of growth partition (b is another constant relating to initial size of the organ). The data suggest now that k is constant for a given temperature: at 28° the larval length x increases by about 1 per cent with an increase of the facet number of 5 to 7 per cent. But it is different at different temperatures. The value of k would then be controlled, *ceteris paribus*, by the Bar gene, and the temperature effect is of the same type as discussed previously, including the possibility of a phenocopic effect. Hersh further is inclined to draw conclusions upon the facet-forming process involved (which belong more to the discussions in a former chapter). From the sigmoid curve which he obtains for the reactions involved (facet-forming reaction) he concludes that it is not a sudden arrest of the facet-forming process in the members of the Bar series in relation to the general growth processes (which had been assumed in Goldschmidt's theoretical analysis of 1927c) but a process that approaches its termination asymptotically. After Goldschmidt's recent work on the vestigial alleles, this result may point in the direction of the possibility that in the Bar case, also, destruction of facet-forming substance at an early stage is involved, especially as Chen has shown that the *Anlage* of the Bar eye is in the beginning no smaller than that of Full eye (see also page 76, the work of Margolis).

Important contributions to the problem under discussion have finally been made by Sinnott and his students in plants. Though the growth of plants is frequently not a closed system as in animals, there are many cases where it follows the same rules and where also the differential growth formula applies (Pearsall,

1927). Such cases, *e.g.*, fruit size, therefore permit a similar treatment, and they are pertinent to our problem when hereditary differential (heterogonic) growth is involved in the form of hereditary control of shape. The problem is then obviously the same as in the *Drosophila* wing (see p. 212) though somewhat complicated by the tridimensional aspect. Nearer to the *Drosophila* wing are the shapes of leaves which, as is well known,

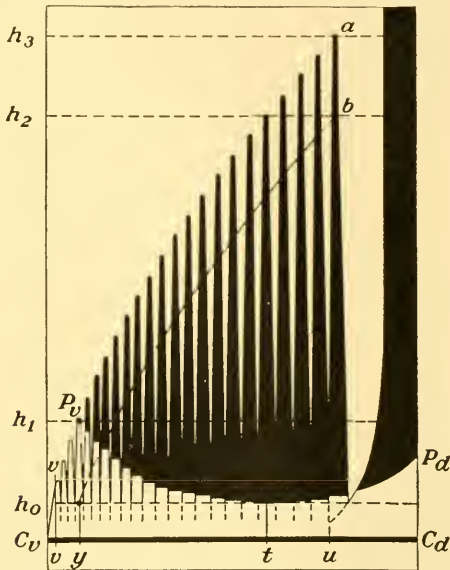


FIG. 39.—Diagrammatic representation of one half of a spread feather germ (collar) of a regenerating feather. The germ has been split along the ventral superficial axis (left) and also in the center of the shaft (right). Barbs and shaft are drawn at right angles to the base of the germ. C_v C_d , locus of primary growth by cell division which is extended to the level h_o ; P_v P_d , a locus of simultaneous pigmentation. Ridges join the shaft at u . (From Fraps and Juhn, 1936, *Phys. Zool.* **9**, Fig. 2.)

are controlled by Mendelian genes in innumerable instances. We have pointed out that size and shape of fruit are controlled by Mendelian genes, sometimes by a single one (tomato, Lindstrom, 1928). In *Cucurbita pepo* (Sinnott, 1927; Sinnott and Hammond, 1930), two independent allelomorphs with cumulative effect (*cf.* the *Drosophila* case, page 212) control the disklike or spherical shape of the summer-squash fruit. In this case, Sinnott (1935*a*) made it clear that shape is not a physiological consequence of size but controlled by independent genes, as is

proved by statistical study of the hybrids between shape races. (As a matter of fact, Lindstrom (1928) had already distinguished between genes for size and shape in the tomato.) A study of development showed, then, that the underlying genes actually control the value of k in the heterogonic growth formula, the coefficient of growth partition. This is well demonstrated in Kaiser's (1935) work on *Capsicum*, where after flowering time,

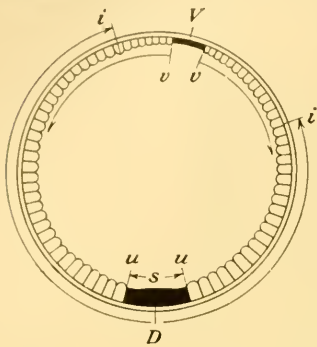


FIG. 40.—Diagrammatic transverse section of the base of the feather germ. D , dorsal limit; V , ventral limit. Initially barbs are laid down from D to i ; later, at v . They are carried by tangential growth from v to u . S , shaft primordium, increasing in the direction of the arrows. (From Fraps and Juhn, 1936, *Phys. Zool.* **9**, Fig. 8.)

fruit shape changes according to the heterogonic growth formula with a definite value of k . A similar case is found in the tomato, where, however, according to Houghtaling (1935), the heterogonic growth is confined to the early development before flowering. In the squash, this period occurs still earlier (Sinnott and Kaiser, 1934).

At this point, the work of F. R. Lillie and his school on the bird's feather ought to be mentioned, though it is as much concerned with pigment pattern as with growth pattern (Lillie and Juhn, 1932; Juhn, Faulkner, and Gustafson, 1931; Juhn and Fraps, 1934). Also, in feather development, a growth by cell division is followed by enlargement of cells. The growth by cell division takes place, however, not after the fashion of a typical growing animal organ but more after the fashion of growth from a cambium zone in plants. This zone is found in the circular collar of the feather follicle, from which at one dorsal point the shaft is growing out while the outgrowing barbs are lined up around the collar. The growing barbs are constantly shifted by a circular growth process toward the shaft and unite with it, when they have reached a certain length. The new supply of barb material is simultaneously pushed up from the ventral side of the collar ridge. Figure 40 of a transverse section through the collar and Fig. 39 showing one-half of the feather germ spread out will help in understanding these relations. Thus, loci of simultaneous age of the barbs are situated at different points on the

individual barbs, *viz.*, nearer the tip in the barbs which grow out more ventrally as compared with those growing out toward the shaft. Lines of equal age are therefore parallel to the base of the collar and stretch transversely across the feather. Now, injections of thyroxin produce pigmentation in an otherwise light-colored feather. Lillie and Juhn showed that with smaller concentrations, pigment appears only near the shaft but stretches across the feather with higher concentrations. Thus, there is within the feather germ a different threshold of reaction to hormones, lower near the shaft and increasing toward the tips of the barbs. These tips have, however, a shorter period of latency and react therefore faster to the proper concentration of hormone. By using these reactivities and injecting different concentrations of hormones at different intervals, many beautiful types of pigment pattern may be produced. Lillie and Juhn believed that the decisive difference in regard to the threshold for response to the hormone was the different rate of growth of the barbs at different points of the collar, which would have reduced a part of the problem to the problem of differential growth. But the recent mathematical analysis of Fraps and Juhn (1936*a, b*; Juhn and Fraps, 1936) has demonstrated that differential growth is not involved in the case. It is very difficult to decide whether or not these results throw light upon the formation of feather patterns controlled by genes. Of course, where purely hormonal differences are involved, as in the patterns distinguishing both sexes, which can be shifted at will in regenerating (or transplanted, Danforth), feathers by adding the proper sex hormone, hormonal action, together with thresholds and some yet unknown rhythmical process may account for the pattern. This is different, however, for genetically controlled patterns like the Plymouth Rock barring of feathers, which does not respond to sex hormones (see Danforth's, 1929, transplantations). Montalenti (1934) has tried to attack this problem. He found that substances in the blood cannot be regarded as responsible for the rhythmical pattern. But there is one interesting relation: feathers in different body regions have a different velocity of growth, and the breadth of a double bar varies proportionally. If we think of the facts regarding the velocity of differentiation of wing scales in butterflies as related to the pattern formation (see page 241), we might conclude that a similar process might take place in the

feather germ. Either a rhythmic production of a growth substance produces in the cambium zone of the feather germ an alternation of quicker and slower cell division with the same result as in moths, *viz.*, that the cells that enter their growth phase later are the ones that can produce the pigment; or, within the cambium, a simultaneous "stratification" takes place very early, resembling the Liesegang ring model (rings in test tubes), and determines which cells may form pigment. In spite of much interesting work, the essential problem—the pattern-forming action of the gene—has hardly been attacked in this case.

Not much more is to be said about the related problem of the agouti hair in mammals in which alternate zones of different pigmentation exist. Dry (1928), who studied this case, ascribed this pattern to an alternation in the hair follicle, conditioning the quantitative aspect of a pigment-forming process in the following sequence: high = black; intermediate = yellow; low = "low black." No information is obtained concerning the causation of the rhythm.

In concluding this section, we may finally refer to work relevant to the problems under discussion but undertaken more from the standpoint of experimental embryology than from a genetical viewpoint. Embryologists frequently have made transplantations of organs between animals of different hereditary size (Harrison, 1924, 1929; Twitty, literature, 1934); and, as a rule, the transplants kept up their own hereditary growth rate, which is to be expected if the determination occurs rather early (see above). But there is also an influence of the host, *i.e.*, the environment visible, which acts upon the transplant by functional, mechanical, or nutritive means. More difficult to explain is the influence that different parts of the organ exercise upon each other: a lens from a larger species working with an eyecup of a smaller species gives a compromise result, each part adapting itself to the different growth rate of the other (Harrison). This belongs, of course, to the difficult subject of regulation. The fact that such regulations usually require contact of the parts indicates at least that principles not different from those involved in ordinary induction may be at work. But there is also a regulation of a different type. If older organs are transplanted into a younger host, or younger ones into an older host, both are influenced so that normal growth relations ultimately result

(Twitty and Elliott, 1934). Twitty explains this regulation by the assumption that the assimilative capacity of younger, faster growing cells is larger than that of older ones, which would mean that they will take out of the available nutritive material a larger share, and vice versa. If this is true, it would follow that the constant k of the heterogonic growth formula controls the avidity of a group of cells to apportion and assimilate a share of the total available food. Regulation then would mean formation of a certain equilibrium in the apportioning capacities of these cells. It is clear that such results do not change the picture derived from the work in physiological genetics but that they add to it a new intermediate step between gene and character: the value of k , controlled by gene action, becomes the ability of cells to secure a definite share of available food.

Obviously, this is only one of the possibilities. It is generally known that hormones play a decisive role in growth, *e.g.*, the molting hormones of insects (Buddenbrock, Wigglesworth), the thyroid and thymus in vertebrates. No doubt, heterogonic growth may also be controlled by hormones, as all the facts concerning thyroid and metamorphosis, thymus and precocious differentiation, sex hormones and growth of secondary sex characters prove. There can be no doubt that among the products of genic action that control the growth pattern, hormones of all the types discussed on page 181 play an important role, including also all types of evocator substances.

2. Symmetry.—Wherever pattern is involved, growth pattern or otherwise, the problem of symmetry will come in sooner or later. Usually, the patterns on both sides of the body are alike, but sometimes they are not. Such an asymmetry may be due to simple fluctuations of the same process occurring on both sides in development. It may also be of a typical hereditary type, which may range from an inclination to asymmetrical distribution to such extreme asymmetries as in the claws of fiddler crabs or other Crustacea. It is known that the problem of symmetry looms large in experimental zoology. There is the problem of the primary symmetry in eggs, the formation of the axes of the embryo which is studied wherever experimentation is made on the early stages of development. There is the problem of handedness as evidenced in innumerable aspects of form and function (see Ludwig's monograph, 1932). There is the statistical

study begun by Pearson and Duncker of right-left correlations to determine their eventual genetic causation. There is the large body of facts relating to symmetry and asymmetry in identical twins (Newman, Bonnevie, Wilder, etc.). The innumerable facts, both statistical and experimental, are relevant to the present discussion only in so far as they permit linking the action of the gene with the process of pattern formation.

Let us begin with certain facts that have been found in the cases that we have already discussed. In the studies upon the scalloping effect in the vestigial wing of *Drosophila* and similar cases, as well as in many cases of bristle abnormalities in *Drosophila*, the following fact was found by all observers. When the very first steps of scalloping are produced either genetically or by external agencies, *i.e.*, the absence of a few hairs at the wing tip up to a small nick, this happens almost invariably only in one wing. This seems to be a rather universal phenomenon, whenever a genic effect is not strictly symmetrical. It may be demonstrated for the unsymmetrical types of the mutants of *Drosophila*, wherever the very low members of a series are known, *e.g.*, scalloped wings of the beaded and beadex type, wing venation of the plexus, delta, extra-vein type, eye defects of the kidney type. It may be demonstrated also for the different phenocopies. Another typical example is the mosaic-like structure of the wings of male intersexes in *Lymantria*, which are shown in Fig. 35.

If we remember now the explanation given for the production of scalloping, the first beginning of scalloping would be produced by a small insufficiency of some growth substance or, reciprocally, by a small amount of lytic substance above the threshold, acting late in wing development. If this were a localized action of the mutant gene, both wings ought to react simultaneously, except for a local variation in thresholds or the like. If, however, the substance in question enters the wing from its base, spreading through the wing, and if this substance is produced in common for both wings, the amount distributed to each wing is liable to considerable variation. For example, if 95 per cent growth substance is available instead of 100 per cent, one wing may receive 46; the other, 49 per cent. If the threshold for scalloping effect is 48 per cent, only one wing will be scalloped. (In case of interpretation with lytic stuff: five units above the

threshold present; distribution, 3:2; active minimum, 2.5.) With further increase of the effect, *i.e.*, still more lowering of the available percentage, the probability of asymmetric distribution with one wing above the threshold will decrease rapidly, and absence of the character on one side will become very rare, though asymmetrical expression on the two sides will continue.

For a general understanding of the process it is rather unimportant whether or not the foregoing interpretation is literally true. The decisive point is that such conditions as quantities of a growth-promoting or retarding substance, thresholds of its action, time and place of its liberation, path of its spreading will provide a system in which a definite constellation will automatically lead to an asymmetrical result. Any gene controlling the master process, which in a given constellation will enforce asymmetric procedure, has, then, an asymmetric action. If this explanation is correct, it follows that in cases such as those just described, other genes (modifiers) may impress symmetry upon the same development by shifting one of the integrating processes, *e.g.*, the value of the threshold or the time of onset of the spreading of the substance. This is actually the case. In the vestigial-wing series, the intermediate phenotypes are rather asymmetrical on both wings. But it was possible to select a symmetrical type from a few rare more symmetrical specimens.¹

A special study of such a case has been made by Timofeeff (1934). The character, already discussed on page 71, is the formation of cross veins in the wing of *Drosophila funebris*. In the case of the scalloping of the vestigial wing, and of the intersexuality in *Lymantria*, there was an asymmetry for both wings, but no large independent variation, because the average amount of effect (scalloping, pigmentation) was about constant for a given genetic constitution. In the *D. funebris* case, Timofeeff thinks that variation was independent in both wings, and asymmetry therefore a statistical result of two independent variables. By selection it was possible to establish lines with a larger right-left correlation, more symmetry. There are, then, genes that may control the phenomenon, just as in the case of the vestigial wings. Timofeeff remarks that one might think of humorally controlled processes and points to the fact that in

¹ Unpublished work.

Drosophila mutants most colorations are symmetrical and changes of structure of organs asymmetrical. He thus comes near to finding the explanation which was given above for the vestigial case and which is also to be found more or less vaguely expressed in other work on the problem.

A similar case occurs also in the work of Boycott *et al.* (1930) on *Limnaeus* to which we shall return immediately and which belongs otherwise to a different type. Here a left-handed line of shells exists, differing by a mutant gene from the normal right-handed one. In these lines, right-handed forms also occur which are not hereditary, although their percentage of occurrence is hereditary. Whether this is caused by modifiers or by different alleles for left-handedness, in some way an embryonic (here cellular) situation near a threshold line must be involved, which might be transmitted or not by some individuals according to genetic conditions controlling a process involved in the threshold. If it should be proved that such lines are actually based upon multiple alleles, the interpretation would have to be parallel to the one for the vestigial case.

We started our discussion of the problem of asymmetry with a case that seemed to be instructive because the asymmetry consisted in existence or nonexistence of the effect on both sides only in the first steps of a quantitative series. However, the most frequently studied types of asymmetry are different in various aspects. We shall now consider three such types.

1. Constant asymmetry of an alternative type. For example, a shell is hereditarily coiled either in a left or in a right-handed spiral. (For examples of this and other types and their details, see Ludwig's monograph and his recent review, 1936.) Here we have the well-analyzed case of *Limnaeus* (Boycott and Diver, Boycott *et al.*) in which a mutant gene changes the direction of coiling (see page 206), and parts of which we have already considered. Occasionally, however, a nonheritable variation to the other type occurs (Lang, 1908; Boycott *et al.*), the frequency of which might be hereditary (see p. 206).

In this case, the cytological basis of the asymmetry is known (see page 206). In other similar cases, we must assume a parallel process, *i.e.*, the presence of a strictly alternative situation at some point of embryonic determination where a determining material for the formation of an organ or for controlling a thresh-

old may go only to the left or to the right. (Ludwig formulates this situation thus: the cells right and left have both potencies of development, and a gene-controlled reaction decides that the higher quantity of a decisive substance appears on one side.) In cases in which one side only is favored by heredity, there must be present some additional mechanism comparable to the one in molluscs which directs a flow or orientation only toward one side.

Other cases, containing at least some genetic information, are as follows. Beliajeff (1931) finds in *Drosophila* that the mutant abdomen rotatum, in the fourth chromosome, has always a dextral effect, whereas the similar third chromosome mutant rotated abdomen is always sinistral according to Bridges and Morgan (1923). In rats, King (1931) found an inherited unilateral microphthalmus with a tendency for development on the right side.

2. Another type of asymmetry is one in which an effect may take place right or left or on both sides. This means that right and left vary independently (no correlation) and that therefore chance may produce the effect on neither side, on both sides, right only, or left only. Such cases are characterized by a right-left correlation coefficient nearing 0. For a number of *Drosophila* mutations, such a condition has been described, *e.g.*, by Guthrie (1925) for eyeless, by Plunkett (1926) for achaete, by Astauroff (1930) for tetraptera. The last author has made a special study of the case of tetraptera. He concludes that here a variability is involved which is more or less independent of the genic constitution and of the environment but is caused by a local variability of the conditions of development. He works this out in a very abstract way, but the facts could as well be described by the action of an embryological process of the type that was derived for the vestigial case. Astauroff thinks that the variations found in regard to the presence or absence of mirror symmetry in identical twins, as studied by numerous authors and explained sometimes by somatic mutation in the case of absence of symmetry (Newman, 1916), are also to be explained by independent right-left variation.

3. Within a genic effect produced on both sides of the body, a certain more or less considerable variation occurs independently on both sides of the body. The pattern is intrinsically symmetric but in detail asymmetric. We mentioned this type for the differ-

ent members of the vestigial series in *Drosophila* (except the lowest and highest) and for the color of the intersexual males of *Lymantria*. In these cases, the interpretation is obvious: the asymmetry is a product of the variability in detail of local systemic conditions which regulate the flow of a growth substance (or other such stuff) spreading from the basis of the wing (see page 222). In other cases, the same or a similar process might furnish the explanation, and the authors who have studied such cases have expressed themselves in a more general way which might easily be converted into a picture of the same type that we developed above. Thus, Haecker (1925) spoke of variations in the internal conditions of the system. Wright (1918), studying the asymmetries in color patterns of guinea pigs, spoke of local factors controlling irregularities in development. The same author (1935) mentions local conditions as causing the asymmetrical expression of polydactyly in guinea pigs.

A different category within this group of phenomena may be assigned to the hereditary asymmetry studied by Breitenbecher (1925) in *Bruchus* (bean weevil). Here a mutant was found that is inherited as a sex-controlled recessive (limited to females but carried by both sexes) in which one elytrum carries two black spots; the other, two red ones. Dextral and sinistral individuals occur in equal numbers, so that it must be assumed that a bifurcated chance process is decisive. It is very difficult to formulate a proper explanation for this type of gene-controlled asymmetry, except by going back to the first stages of development of wings. (A parallel case in *Drosophila* is being investigated by the author.)

The oldest example of this type was already known to Darwin and has been studied genetically by Przibram (1908). In cats, individuals occur with one blue and one yellow eye. This asymmetry is hereditary, and among the offspring of individuals with blue on the right side individuals with blue on the left may also occur. The inheritance of extra toes in poultry and guinea pigs is of the same type. Many cases of this type occur in man where much work has been done, as the problem becomes important when identical twins are involved. Danforth, Newman, Dahlberg, and others have discussed these problems and presented facts. Dahlberg (1929) has tried to formulate an explana-

tion closely following Goldschmidt's suggestions on the basis of a chance distribution of formative materials.

There should finally be mentioned some recent non-genetic experiments by Darby (1934) on the old problem of asymmetry of claws in Crustacea. Przibram (1901) had shown that, after removal of the large snap claw, at the next molt the pinch claw produced a snap claw, and a pinch claw was formed from the stump of the old snap claw. Much work has been done since on the same and similar problems, without leading to an understanding of the processes involved. Darby removed first one claw and then the other after different time intervals. Thus, he found the critical time (about 30 to 42 hr. after the first operation) at which the fate of the regenerate will be decided. By proper experimentation he could thus shift the process so that on both sides pinch claws or on both sides snap claws or on both sides intermediates were formed. He refers this change of asymmetry into symmetry to the relative times of production and to the quantity of two morphogenetic substances *A* and *B*. The factors controlling them he calls generally environment and points out that here environment supersedes the effect of the genes. From this he concludes that the genes are responsible for the production of the substances, and the environment for their quantity. If we substitute for environment the combination of integrating processes, all of which are gene controlled in normal development and all of which may be shifted by external agencies, we come again to the point of view regarding symmetry and asymmetry that we have developed above.

Ludwig (1936) has discussed the same experiments and attempts an explanation which is different from Darby's (and a similar one by Dawes, 1934). His argument is as follows. The claws have hereditarily an alternative norm of reaction (pinch or snap). In regeneration, the decision falls in favor of the alternative for which at this moment the larger quantity of determining material is available (see Lymnaeus, page 224). This material is being increased because its production is controlled by the type of claw that is developing. A formal explanation for the rest of the experiments may be derived this way. Also, this point of view may be expressed in the terms developed above. But as no genetical facts are known that might be linked with the experimental results, this short review may suffice.

3. **Special Patterns Superimposed upon the General Pattern (Secondary Tertiary, Etc., Patterns).**—Two examples will show what is meant by the foregoing heading. The general pattern of a *Drosophila* wing is given by the arrangement of veins and spaces between the veins; form and arrangement of hairs; and the typical proportions, shapes, and curvatures of the wing. In the series of mutants of the vestigial or beadex type, or similar series, this primary pattern of the wing is not affected or only as far as certain regulations and readjustments are necessitated locally as a consequence of the abnormal development. But an additional new pattern is created, the typical shapes of the partly destroyed, scalloped wings in different members of the series. For a second example: in the gypsy moth or *Promethea* moth, female and male wings have essentially the same primary pattern of bands and spots. But in the male, this pattern is overlaid by a dark pigment covering more or less the primary pattern. We consider these types first because they are simpler and also better known genetically.

If we look at a series of mutants of the vestigial series in *Drosophila*, we find a definite pattern in each, *e.g.*, the pattern type Notched or Strap (see Fig. 19). These patterns are characterized by the following features.

1. A certain regularity is observed if a series of stages is compared. The scalloping begins at the tip of the wing; it destroys large parts of the wing before the alula and posterior cell are affected; it destroys the central part of the wing along its entire length last, beginning at the tip.

2. There is a certain irregularity: the details of the scalloping are rather variable, and often no two wings exactly alike. The two wings of one individual vary independently in regard to the form of scalloping (not in regard to its amount), and symmetry is reached only in the lowest and the highest grades of scalloping (see, however, page 223). But for a given mutant type the average amount of destroyed area is constant within certain limits. We have already given the interpretation of the phenomenon of scalloping as derived from the study of development: an insufficiency of a substance needed for growth or the production of a lytic substance above a certain threshold produces the degeneration that leads to scalloping. If we consider, now, the pattern according to which the different effects occur from nick

up to vestigial, *e.g.*, by drawing a typical series of these patterns together into the contour of a normal wing (Fig. 41), we see a way of understanding these patterns. If a definite amount of the supposed growth substance diffuses into the wing from its base—to use only one of the alternative explanations, the other being its reciprocal—the path or bed of such a flow will be determined by the structural, physical conditions of the organ, and a more or less definite bed will be prescribed. If this flow ceases at different times before the whole wing is covered (insuffi-

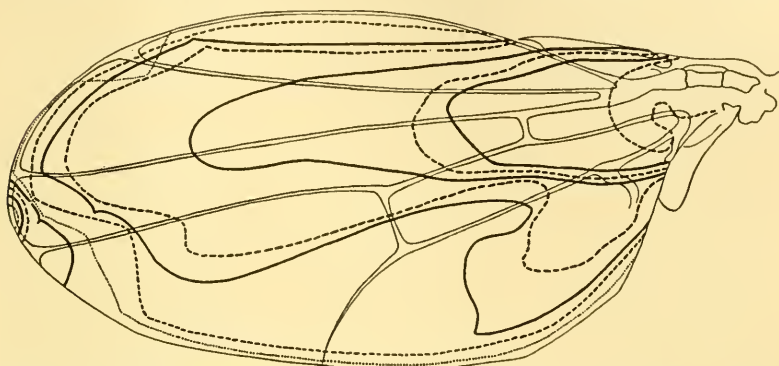


FIG. 41.—Wings of a series of *vg*-alleles drawn together to demonstrate the path of the destructive process.

cient amount of the substance), the rest of the wing will degenerate, and the contour of the degenerating area, of the scallopings, will represent the front line of the flow and the moment of its being stopped. The whole series of stages of scalloping, then, furnishes a cinematic picture of the bed along which the substance in question spreads. The pattern produced is therefore a function of the amount of spreading growth substance controlled by a mutant gene (or by a phenocopic effect) and of the structure of the organ providing the drains and obstacles, shortly to be described as the *conditions of the system*. In case of explanation by spreading of a lytic substance, the moving picture would be the reciprocal of the foregoing: the filling in of the wing area with this substance, beginning at the tip.

This interpretation recalls at once a case that we have already described, the pattern upon the wings of intersexual males of the gypsy moth (Fig. 35). We remember that here, too, the facts led to the conclusion that the determination of scales in the male

is produced by a stream of a substance entering the wing from its base and spreading in a radial direction without fixed beds but not completely without order. Also, in this case, there was a relation between the quantitative features of this flow and the resulting pattern. Either the time allotted to the spreading of the substance determines how much of the wing surface will be covered, *i.e.*, the relative amount of male and female area; or the amount of substance available is responsible for this. In both cases, then, we have a rather irregular pattern effect of different arrangement in detail, controlled by the action of genes. The genes in question do not, however, control the pattern directly but reactions of definite speed, leading to production of definite substances at definite times or in definite quantities. The diffusion of these substances into the organ—generally described as a determination stream—in beds prescribed by the structure of the organ, together with the time of onset or quantity of the flow or both, produces in one way or another the resulting pattern. There can be no doubt that this simplest method is the most frequent one in general processes of formation of embryonic patterns. An indication of this will be found in the fact, also emphasized by Timofeeff (1934), that most of the mutants of morphological characters in *Drosophila* tend to show the type of asymmetrical behavior just described for the vestigial case. Color mutants, however, the genes for which do not act through induction of pattern formation, are symmetrical in effect. To this should be added, as a nice check, the fact that vermilion eyes, which we know (see page 186) to be formed partly by an inductive process of the hormonal type, are frequently found in asymmetric expression.

The same material may lead one step further. We have stated that a series of facts similar to those concerning the vestigial wing of *Drosophila* was found for the truncated wing (see Goldschmidt, 1937). In this case, the degeneration of tissue as a result of insufficiency of some substance takes place below the wing epidermis, which remains intact. The wing margin is then retracted beyond this degenerating area (Fig. 42), caves in, and forms the truncate wing, which also is known in a series of increasing conditions, caused genetically as well as by phenocopic effect. Here, now, we are facing a perfectly regular pattern, *viz.*, the dumpy shape with curved margin of the *Drosophila* wing

caused by a gene-controlled process which is not directly concerned with pattern but leads automatically to a pattern as a consequence of the conditions found in the system, here the wing *Anlage*.

A closer study of the wing pattern of the intersexual gypsy moth leads to another insight. In spite of the general aspect of lack of order in the flow of the determination stream, we find



FIG. 42.—Three stages in the development of a dumpy wing in *Drosophila* from a normal pupal wing. (From Goldschmidt, 1937, *Univ. of Calif. Publ. Zool.*)

occasionally definite relations to other elements of the wing. It is not surprising that frequently the wing veins may form the edges of a pigment tongue. But more important is the fact that sometimes a pigment streak ends along one of the zigzag bands (Fig. 43) (see also Kuehn and Henke, page 198). The impression is that these bands stopped the further progress of the stream. In this case, it is only an occasional happening (see Minami, 1925). Conditions within the wing *Anlage* might easily be such that a determination stream would always be stopped by a band, *i.e.*, by some part of the structure of the organ which is determined

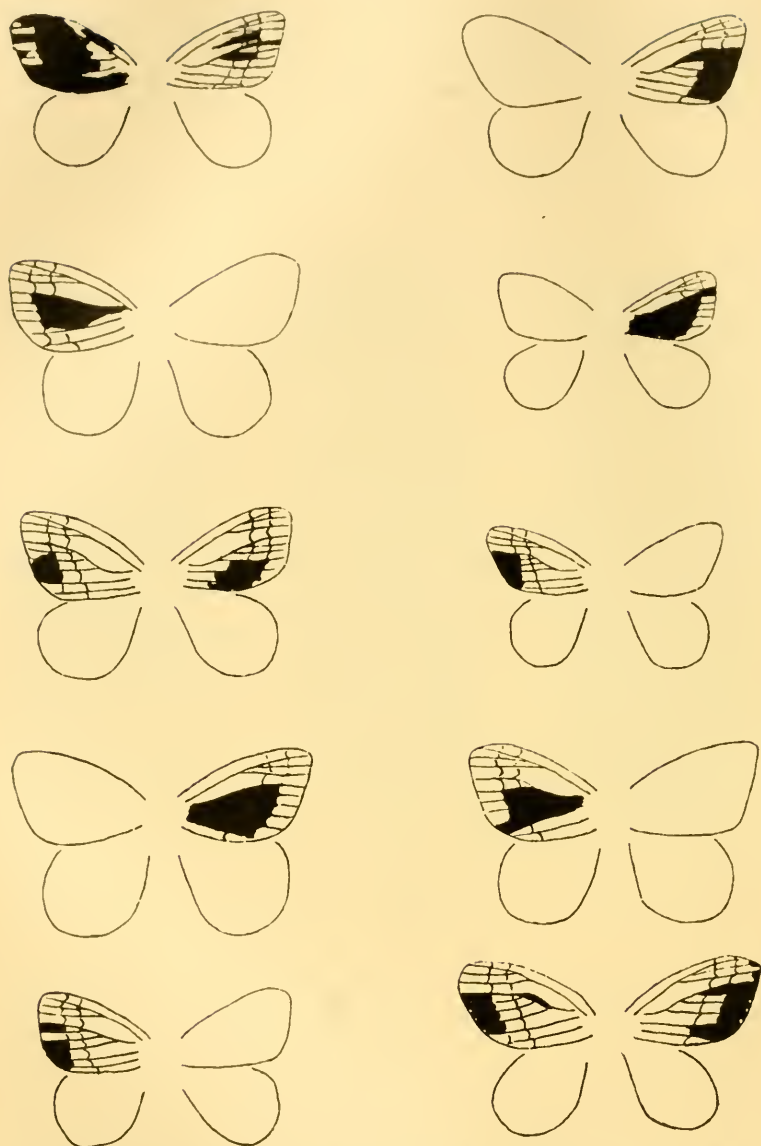


FIG. 43.—Outlines of wings of intersexual males in *Lymantria dispar* to demonstrate the relation between color pattern and veins and bands. Female parts black. (From Minami, 1925, *Arch. Entwicklmech.* **104**, Fig. 3.)

independently. In this case, the same type of flow of a substance across the wing would lead to a perfectly regular pattern.

There can be no doubt that many patterns found in our models, the wings of *Lepidoptera*, are of this type. Examples will be discovered wherever mutant genes do not change the original pattern of the species but superimpose upon it a process that leads to a secondary pattern. This will frequently be the case with sexual differences and also with mutants of the type of



FIG. 44.—Pupal wing of *Papilio podalirius*. The part of the wing to the left of the undulated line will degenerate, leaving only the tail. (From Sueffert, 1929, *Zeitschr. Morph. Oek.* **14**, Fig. 9.)

melanisms where a pigment covers the preexisting pattern in a definite degree, which might be quantitatively graded by the action of different allelomorphs or genes. A number of such cases have been analyzed genetically (Goldschmidt 1921*b*, 1924*a*; Federley, 1920; Kuehn and Henke, 1929–1936), but little else is known that would permit going beyond these general statements. The most important additional fact is that similar patterns to those produced in these cases by genes may also be produced by temperature action, *e.g.*, melanic patterns of one sex in *Gastropacha* (Standfuss, 1896), *Lymantria* (Kosminsky, 1909; Federley, 1907; Goldschmidt, 1922*b*); general melanism in *Habrobracon* (Schlottke, 1926); and *Ephestia* (Kuehn and Henke, 1929–1936). In this group belong also such secondary

patterns as series of ripple-like lines between the main elements of the pattern. They may be partly the expression of such embryonic structures as the network of blood sinuses, as suspected by Goldschmidt (1920*d*). But thus far this type of secondary

pattern has not yet been studied genetically or experimentally. For a general discussion, see Henke (1935).

One more case might be mentioned in this connection which belongs generally to the type represented by the wing form of *Drosophila*. It is known that many species of *Papilio* have tails on their hind wings; it is further known that in some species only males have tails; and, further, that in some of the polymorphic species, females may have no tails, short tails, or tails according to the presence of different Mendelizing genes (de Meijere, Fryer, etc.; see Goldschmidt, 1931*d*). A similar effect may also be produced by action of temperature (Standfuss) or shock (Poulton).¹ Sueffert (1929*a*) showed that the development of this wing pattern—formation of tails—is such that first a wing of normal contour is formed, from which the tails are cut out through a secondary process of degeneration (Fig. 44). It is needless

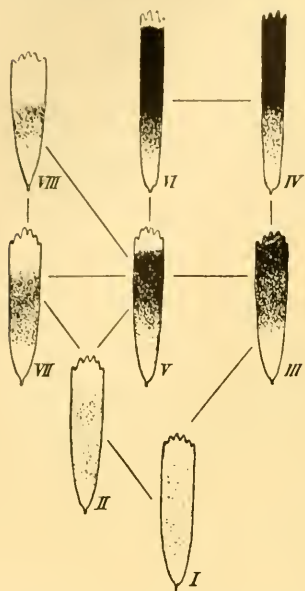


FIG. 45.—Relation between form and pigmentation of scales in the flour moth. Eight types of pigmentation. IV and VI form the dark bands in wild type; VIII forms the light pattern elements. The others are found in the background. (From Kuehn, 1936, *Naturwiss.* 24, Fig. 5.)

to discuss in detail the generalization that here a pattern-forming process may be understood on the same lines as in our former examples.

In describing the case of the pattern of intersexual wings, we repeatedly mentioned the fact that male areas have scales of the typical form for males and, similarly, female areas, female scales in type and arrangement (Fig. 46). Here we are facing another important point. One and the same process—the spreading

¹ Poulton gave a different explanation of Van Someren's material; see Goldschmidt, 1931*d*, p. 475.

determination stream—leads to formation of pigment, eventually to a formation of pattern and simultaneously to quite typical details of morphogenesis, here in the development of scales. Rather similar facts have later been found in the flour moth, where a definite relation exists between pigmentation and form of scales (see Kuehn, 1932; and Fig. 45). If we add that Feder-

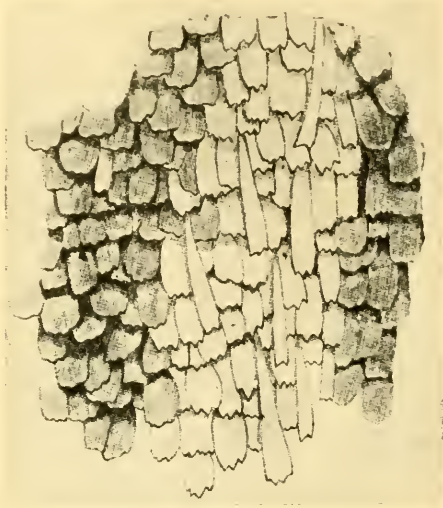


FIG. 46.—The scales upon an intersexual mosaic spot in *Lymantria dispar*. (From Poppelbaum, 1914, *Zeitschr. ind. Abstl.* 11.)

ley (1907) had produced typical changes of scale form by temperature action, we see that we are facing the same series of interrelated facts: gene action or phenocopic action→production and definite course of determination stream→general and special morphogenetic pattern. Thus, the series of facts mentioned in this chapter and their logical connection furnishes an important step toward the understanding of the action of genes in controlling pattern.

At this juncture we might report upon the much discussed but not yet transparent case of the scute allelomorphs in *Drosophila*. This large series of alleles produces a definite pattern of bristles, some of which have been discussed. Definite bristles are absent in each case, but with a certain amount of variation. We shall not mention here the implications of this case as far as the theory of the gene is involved; that will be done in a later chapter. We

are reporting only such parts of the discussion as have to do with the production of the specific bristle pattern by the action of genes, whatever they are. The school of Serebrovsky (Dubinin, Lewit, Agol, etc.) which has furnished most of the data has used them only in an attempt to analyze the gene itself (see page 295).

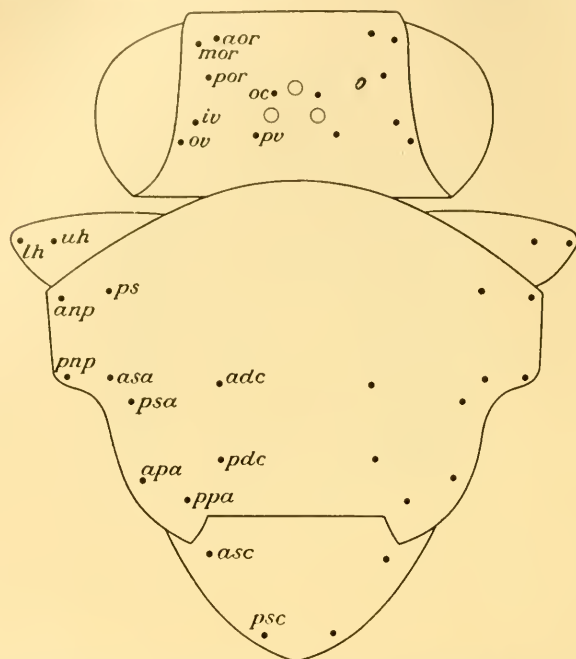


FIG. 47.—Location of bristles of *Drosophila melanogaster*. *aor*, *mor*, *par*, anterior, middle, posterior orbitals; *oc*, ocellar; *pv*, postvertical; *iv*, *ov*, inner, outer verticals; *uh*, *lh*, upper and lower humerals; *anp*, *pnp*, anterior and posterior notopleurals; *ps*, presutural; *asa*, *psa*, anterior, posterior supra-alar; *apa*, *ppa*, anterior, posterior postalar; *adc*, *pdc*, anterior and posterior dorsocentrals; *asc*, *psc*, anterior, posterior scutellars. (From Plunkett, 1926, *Jour. Exp. Zool.* 46.)

Sturtevant and Schultz (1931) and Goldschmidt (1931b) tried to look at the case from the standpoint of pattern formation, and Child (1935, 1936) has recently attacked the problem also.

The work in question is based upon the idea that these different alleles produce a definite pattern of bristles by removing specific individual bristles. If this is done in an orderly way, the phenotypes of the different alleles may be arranged in a corresponding seriation. Figure 47 represents the bristles in question on head, thorax, and scutellum of *Drosophila*, with their respec-

tive names. Figure 48 shows for 15 alleles which bristles are affected by the respective genes. The fact that such an arrangement is possible demonstrates a certain order in the scute effect, *i.e.*, a pattern, and in addition an orderly behavior of the different patterns. This latter order is brought out in the experiments of the Russian authors who analyzed all the possible compounds of these alleles and found that the compound always showed only an effect upon those bristles common to both types entering the

		<i>l</i>	<i>h</i>	<i>mr</i>	<i>dc</i>	<i>lv</i>	<i>sa</i>	<i>l₃</i>	<i>ov</i>	<i>vt</i>	<i>pnp</i>	<i>ps</i>	<i>a</i>	<i>np</i>	<i>por</i>	<i>pa</i>	<i>aor</i>	<i>mor</i>	<i>oc</i>	<i>cx</i>	<i>pv</i>	<i>sc</i>	<i>st</i>	<i>h</i>	<i>l₂</i>	<i>w</i>	
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FIG. 48.—The step allelomorphism of the scute alleles. Abbrev. as in Fig. 47. *mr*, microchaetes on thorax; *vs*, ventral bristles; *cx*, coxals; *w*, crumpled wings. (From Dubinin and Friesen, 1932, *Zeitschr. Biol. Zentralbl.* 52.)

compound. This led to the arrangement as figured, which has been called a step arrangement.

There is, of course, no sense in analyzing this case from the standpoint of pattern production, if these primary facts do not hold. They have been accepted as valid by Sturtevant-Schultz (1931), though their seriation is a little different. In recent papers, G. Child (1936), however, doubts if there is a problem of pattern involved at all. He bases this conclusion upon the following facts. In temperature experiments on one scute line, each bristle reacts independently of every other; it is determined independently for each bristle whether it will be present or absent. Flies raised at 14° show variations of some bristles, the same bristles being constant at higher temperatures, and vice versa. Such flies raised at different temperatures appear as different from each other as do two different scute alleles raised at the same temperature. From this he concludes that the appearance of a pattern is an illusion, produced by looking at the statistical differences in mean numbers instead of at the condition of the individual fly, in which the distribution of bristles may differ from that of any other individual.

I do not think that these arguments are valid. We know from all the cases presented above that by temperature effects the phenotype of one type may be changed into that of a mutant type (phenocopy). This does not mean, however, that no pattern is involved in the production of those types but rather that the process of pattern formation is of such a nature that it may be shifted in different directions through external (temperature) or internal (modifiers) changes. The cases that have been described illustrate this elementary principle. It is not an integral part of the pattern conception that a pattern-forming process is invariable; it is, indeed just as variable as any other process, and its laws will therefore become better visible in statistical treatment than in the study of individual cases. Child himself finds that at a temperature used by the Russian authors the effect upon bristles agrees with the seriation given by these authors. Apparently, a bristle pattern is actually involved, though it may be shifted by modifying agencies.

A second point to be clarified is the type of pattern involved. If we think of our former discussions regarding the outlet of the determination stream (called center of diffusion in Plunkett, 1926, and Child's papers), the following different situations might be found: (1) There is one point of outlet, and the whole pattern in all cases (barring now the variations) is the consequence of the conditions of the whole system prescribing the bed of the determination stream. (2) There are a number of outlets, and their combined workings with the general conditions of the system in time (time of opening of the outlets, time of flow) and space (direction of the stream, eddies, obstacles, etc.) will control the resulting pattern. (3) Each bristle corresponds to a separate point of outlet, comparable to the different typical spots in a piebald pattern. Then there would be no space element, a flow, but only a time element—opening of the outlet—and a threshold element—sufficient quantity of determining stuff for bristle formation (or bristle destruction). The first two possibilities may be combined with the peculiarities met in our former cases: the bed of the stream might be thoroughly fixed (many moths); it might be variable within certain limits (the vestigial series); and it might almost be left to chance (the intersexual wing of *Lymantria*). In the last case, each individual would be different, though a statistical treatment would reveal an average pattern.

In the case considered as 3, there was no determination stream that could have different beds. But the causative agent for the functioning of each center of diffusion (at each bristle) might change in regard to the time of the onset of action (or the threshold), and there might be more or less order in this respect; this would give the same phenotypic result as the different types of a determination stream. Sturtevant and Schultz (1931) thought of the type with one point of outlet. Goldschmidt (1931*b*) tried to derive from the facts a system with five such points. Dubinin and Friesen (1932) as well as Child (1936) think, however, that the actual variability of the behavior of the individual bristles does not show the type of correlation that would be required if a determination stream should coordinate the behavior of groups of bristles that it would have to reach in a definite order. This is a potent argument in favor of the possibility mentioned under 3. The recent work of Nujdin (1936), at least in part, supports these conclusions. He made a special study of the correlation of different areas by comparing their behavior in mosaics, exhibiting different areas containing bristle- and hair-affecting genes (scute 8). It is to be remembered that the mesonotum (dorsal thorax and scutellum) is derived from one pair of imaginal disks. The sternopleura might develop from either the dorsal or the ventral mesonotal disk, and the humeri are formed from an independent disk. He found that all areas derived from different disks behave independently. Within the mesonotum he finds nine areas on each side that behave as units in regard to mosaicism. This means that in the differentiation of the mesonotum at some time a subdivision takes place which results in a pattern of the surface of the mesonotum. According to Nujdin's description, some fields in this pattern contain only one, and others two, bristles (nine areas and 11 bristles). This, then, means that most of the bristles, but not all, are found in areas that have been formed as independent parts of a pattern. It has to be added that within a given area a stronger correlation exists in an anterior-posterior direction. This means that the bristle pattern is the result of a formation of areas in a definite pattern, a formation that is bilaterally independent, proceeds generally in an anterior-posterior direction, and takes place almost simultaneously. If this description is correct, one might conclude that it is not a series of determination streams that are involved

but a more or less simultaneous stratification of the whole field into areas followed by the bristle-forming reaction. In a general way, these results agree with those of Rokizky (1930).

The question is what this would mean for the problem of bristle pattern. This pattern means the formation or not-formation of one (or two) bristles within certain areas. (It might also be a destruction of bristles after their formation, as suspected but not yet proved.) Child has found that all individual bristles in a given mutant line have the same temperature-effective period. This indicates that the bristle pattern is not concerned with the moment of bristle formation, as expected from the foregoing considerations. But there is an important item in Child's last paper: in different mutants of the series there is a difference in regard to the sensitive periods and to the time of development.

This leads to the last part of the problem. Goldschmidt had assumed that a determination stream is involved, but he was careful to point out simultaneously that this assumption is not a necessary part of the argument, which holds also in case of independent determination of each bristle. The decisive point was to explain the steplike arrangement of the phenotypic effects in the series. This would be completely explained if the different areas of the pattern in the mutants had a different time of differentiation, the beginning as well as the duration of which is controlled by the different alleles. Expressed in terms of determining substances, this would mean that the outlets would open at different times in the different areas or that the velocity of differentiation became different in the areas or a similar process involving a time element. Such a system, as worked out by Goldschmidt in a model that might be changed in many directions (see also Friesen and Dubinin who constructed a similar model in order to criticize it), accounts sufficiently for all the facts in a general way. The observation of Child, which was just mentioned, is highly in favor of such an explanation by relative rates of some processes. We refrain, however, from going into more details. If Child's (rather improbable) claim that the step order of the Russian authors and also of Sturtevant-Schultz is of no value were justified, any discussion would be superfluous. Future studies will be necessary to clarify the problem.

4. Composite Patterns.—Considering rather simple types of patterns, we discussed cases where the limiting factor for the spreading of a determining stuff was given by a pattern already present in the system, *e.g.*, the zigzag bands of the *Lymantria* wing. The analysis of the effect of mutant genes will more frequently meet with the simpler type of the processes because Mendelizing genes affect more often late details of morphogenesis. But analysis of more complicated cases of pattern has also yielded considerable insight. Thus far, however, it has not

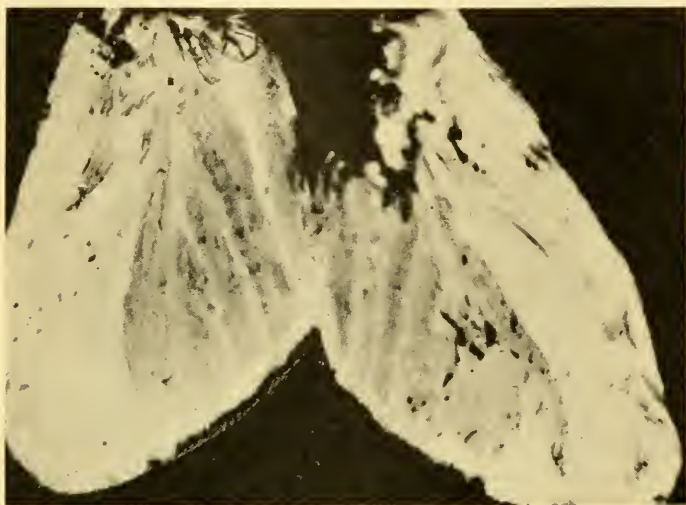
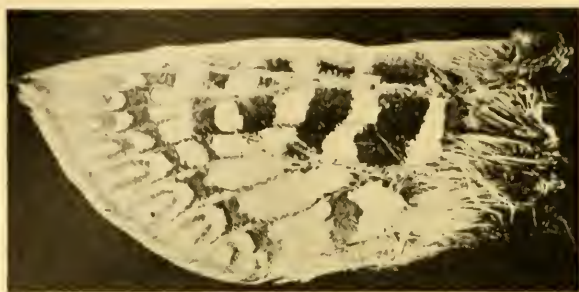


FIG. 49.—Pupal wings of intersexual males of *Lymantria dispar* after drying, showing the finished white scales and the soft collapsed scales in the later dark parts of the wing. (From Goldschmidt, 1923, *Arch. mikr. Anat.* **78**.)

been possible to fit all the partial processes that have been found into one simple coherent picture. The attack upon this problem has been done entirely with the Lepidopteran wing as material, except for a few facts relating to mammals. There are two types of facts of primary importance which thus far could not be properly linked, though this is required for a full understanding in the study of the lepidopteran wing.

a. General Embryological Features.—In studying the development of patterns in the lepidopteran wing, Goldschmidt (1920*d*) found one general rule which may be stated as follows: A long time before pigment is formed and before the scales are perfected, a different rate of differentiation becomes visible in regard to the

later pattern: parts that later will carry dark pigmented scales show a slower differentiation of the scales than parts that will later carry white or yellow or red scales (distinguished by con-



a



b

FIG. 50.—Pupal wings of the swallowtail, *Thais polyxena*. a, fully developed; b, before pigment formation, later white parts with finished scales, later pigmented parts collapsed. (From Goldschmidt, Fig. 48.)

taining uric derivatives or carotinoids or air). This can be detected only during a very short period of differentiation: if a pupal wing at this stage is dried, the already differentiated scales remain erect; the undifferentiated scales on later dark areas, however, collapse because they are soft bags filled with blood.

Thus, the main features of the future pattern become visible in the form of a relief of protruding and of flattened scales. Figure 49 shows such a stage from an intersexual wing, the later male parts being represented by the valleys of the relief. Figure 50 shows a similar condition in the wing of a swallowtail butterfly, compared with the finished pattern; and Fig. 51, a similar stage in the formation of the eyespot in a Saturnid moth. This differential velocity of differentiation within different parts of the pattern was found in numerous different objects from diversified groups,¹ including also the zigzag bands of *Lymantria*. It was,

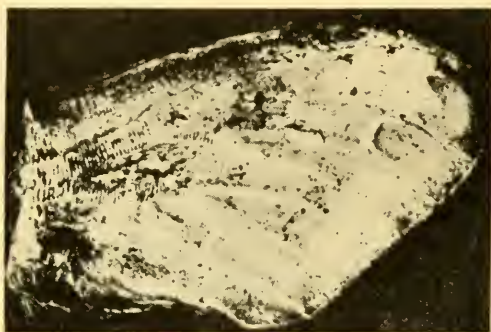


FIG. 51.—Dried pupal wing of *Samia cecropia*. Region of the later eyespot with crescent of white scales, which are finished and erect. (From Goldschmidt, 1920, *Arch. Entwicklmech.* 47.)

however, not observed in Kuehn's work on the flour moth, the reason probably being that the very quick development of this form makes it difficult to find the short stage when the phenomenon may be made visible.²

In the flour moth, moreover, Kuehn's students Koehler (1932–1935) and Braun (1936) found another nearly related fact. At an early stage of development of the wing, the place of the future zigzag bands is indicated by a zone of more numerous mitoses. Two such waves of increased mitotic activity spread across the wing: one in the hypodermal tissue; a second, in the scale-forming cells. If a mutant (or a phenocopy) has a different arrangement of the bands (shifting toward the base or the tip), the pattern of mitoses, indicating the later dark areas, is correspondingly shifted (Fig. 52). In addition, it was found that the

¹ Mostly unpublished work by Goldschmidt and Sueffert.

² It has been found meanwhile by W. Braun in the author's laboratory.

number of scales formed in the later dark areas is larger per unit than in the light areas. A difference in the relative increase of the number of scales in light and dark areas was not found. These facts are in perfect harmony with Goldschmidt's discoveries (a point not realized by the flour-moth investigators); the occurrence of many mitoses means that the cells in question have not yet

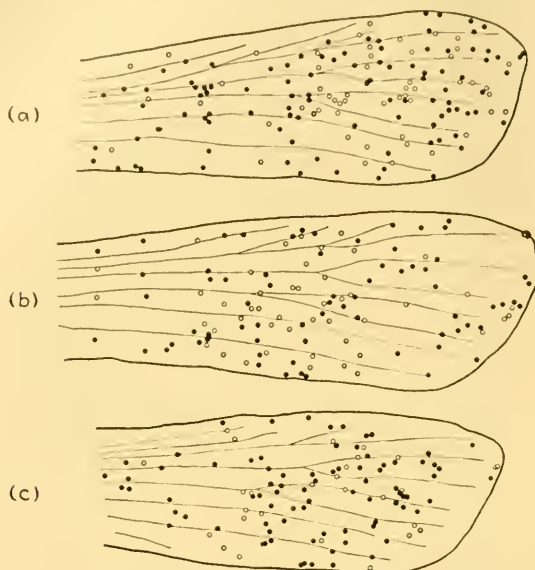


FIG. 52.—Pattern of mitoses in young pupal wings of the flour moth, 66h. a. normal; b, shift toward the center in the mutant with narrow field of symmetry. (From Braun, 1936, *Arch. Entwicklmgmech.* **135**, Fig. 7.)

reached the end of their multiplication period, after which growth and differentiation (formation of scales) begins. They are therefore retarded in differentiation as compared with the cells that do not divide further. Another fact has been found by Koehler which falls in line: in the flour moth the wing rudiment folds up at a certain stage, and these folds coincide roughly with the situation of the future zigzag bands. This, again, agrees with Goldschmidt's observation, as the softer, less differentiated parts of the pattern, located in the zigzag bands, which will still undergo mitotic division, are the natural lines of folding.

We spoke of different speed of differentiation of the scales in the different areas of the pattern. This must not be mistaken for different growth. This is roughly identical all over the wing.

The difference is actually found in the velocity of hardening of the chitin. As pigment is deposited in the chitin in colloidal solution, a hardened scale cannot be pigmented any more, and therefore the speed of hardening, different in different areas, leads to the pattern of pigmentation. Recent work in the author's laboratory has confirmed these basic facts, which therefore cannot be overlooked any longer.

These two groups of facts together show that a primary pattern has been formed early in development for the whole wing as a unit. The pattern consists in the creation of zones of differential velocity of differentiation, which later will lead in some way to different pigmentation and sometimes shape and structure of the scales. This unit pattern is influenced by mutant genes. (Sexual difference might be included in this statement, because genetically the difference is of the general type of a mutational difference.) Can we now conceive of the gene-controlled process that leads to the formation of such a complex pattern? In the case of the intersexual wing, we have found the answer: here the pattern of areas of different speed of differentiation was conditioned by the determination stream spreading from the wing base across the wing. There is no reason to suppose that the process is a different one (in principle) in the other cases. What has to be explained, obviously, is why the production and spreading of such a substance leads to induction of definite growth velocities only at definite points or, using an expression previously introduced, why this induction becomes stratified.

b. Pattern Localization.—In Goldschmidt's first publication on the subject (1920*b*), a rather generalized formulation was applied to this problem. The special arrangement of the parts of the pattern was referred to as the arrangement of the outlets of pigment, which now has to be defined as the arrangement of points from which the determination stream starts. It was known from the genetic analysis of different patterns that a number of genes may be concerned in controlling this arrangement. Forthwith an attempt was made (Goldschmidt 1920*d*) to change experimentally the processes involved by injuring the young wing in different ways, setting defects, etc. But only the very beginnings of success were attained. As is now known from Henke's work (1933*a*) upon the same material and using partly the same methods, the lack of complete success was due to

ignorance regarding the actual situation of the sensitive period, after the end of which the pattern cannot be changed. In recent years, Kuehn, Henke, and their students have successfully attacked this problem.

These experiments are partly based upon an interesting progress in the study of the morphology of such patterns, due to Schwanwitsch (1924-1929) and Sueffert (1925-1929). These

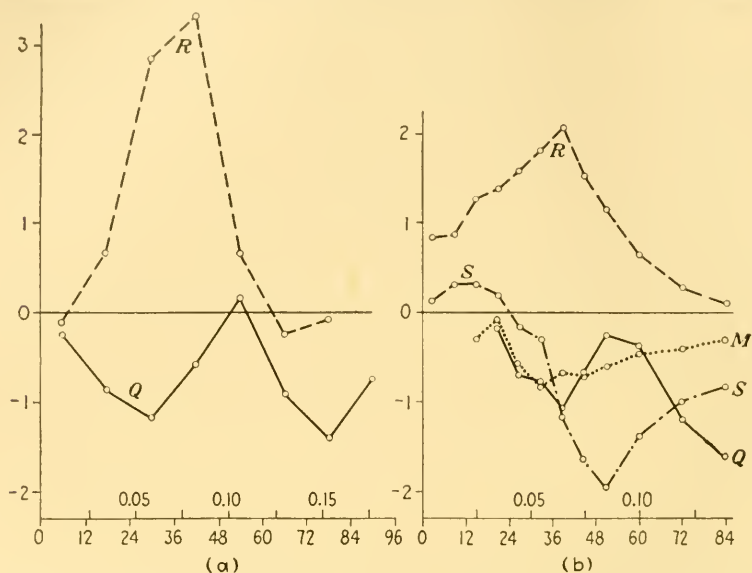


FIG. 53.—Sensitive periods for the dark pattern elements in flour-moth pupae. *R*, number of dark scales in the marginal spots; *M*, in the central spot; *Q*, the dark bands; *S*, the "shadows." Abscissa: age of pupa in days and in fractions of whole length of pupal period. Ordinate: units of the controls. *O* = *M* of the controls. (From Kuehn and Henke, 1936, *Abh. Ges. wiss. Goettingen*, **15**, Fig. 87.)

authors showed that within a given group of Lepidoptera (nymphalids, Schwanwitsch, Sueffert; saturnids, Henke (1928, 1933*b*, *c*, 1936), the wing pattern may be reduced to a simple arrangement of elements that are invariably found. Figure 36 showed diagrammatically such a case; the central field of symmetry with the two symmetrical bands is noticeable. Outside lies the ocellar system, followed by the marginal bands. Near the roots of the wing are the so-called hollow elements.

Sueffert (1925) and Kuehn (1927) further showed that in temperature experiments these different "fields" reacted inde-

pendently: a definite treatment may change only the field of symmetry or another field. In addition, the temperature-effective period may be situated at different points of development (Kochler and Feldotto, 1935, Wulkopf, 1936). Figure 53 shows the curves for the degree of expression of different elements of the pattern in the flour moth after heat treatment at different times of development; the maximum effect marks the sensitive period. In addition, Kuehn and Henke found in the flour moth a number of mutants which affected definite parts of this system. We have mentioned one that enlarges the symmetry field. Such mutants had also been known for other objects. Thus, Goldschmidt had found a recessive mutant in the gypsy moth, in which all the zigzag bands belonging to the so-called symmetry system had disappeared; another that affected only the marginal markings; another affecting the symmetry field but not the zigzag bands; and others affecting general color independent of pattern. A case of a similar type is the color pattern of coccinellids. In *Epilachnia chrysomelina*, Tenenbaum (1933) showed that many details of the individual spots are controlled independently by different genes. The next step was made when Henke 1933a succeeded in changing details of pattern by operating upon the young wing.

By cutting off parts of the imaginal disks or burning parts before final determination had taken place, Henke succeeded in shifting elements of the pattern in the *Cynthia* moth. The bands of the symmetry system are here somewhat differently arranged on fore- and hind wing. Proper operations may change each of these types into the other one. The formation of the bands after operation showed clearly that they are formed at the borders of the central field, *i.e.*, at the edge of a determination stream, as illustrated before for the flour moth. Also, other elements of the pattern could be shifted; *e.g.*, the crescent-like spots could be subdivided into two; the marginal bands could be changed. Though every detail may not yet find a proper explanation, it is shown, in general, that the process of pattern formation occurs by movement of substances in definite paths which are set by the conditions of the whole system and may be changed by removal or destruction of parts.

Similar experiments by Kuehn and associates upon the wing of the flour moth and of *Abraxas* have already been reported, and

we saw how they demonstrated the existence of a determination stream, comparable to the one discovered in the *Lymantria* wing.

All these facts now lead to the decisive question: How can the action of the genes be linked with these different aspects of pattern localization? In his detailed analysis of the problem, Goldschmidt (1927*c*) stated thus the general facts and viewpoints that have to be taken into account whenever this problem is being attacked:

1. The pattern of a lepidopteran wing is formed by the definite arrangement of areas, which contain scales different in color and partly in structure. These areas may be chemically different, *e.g.*, contain melanin, guanin, carotin, etc. They may be different only in regard to quantity, *e.g.*, contain different concentrations or grades of oxidation (or reduction) of melanin. They may be different physically in regard to the form of scales or their surface structure (optical colors).

2. Viewed as a whole, the patterns result from combination of rather few elements: specifically colored or structured scales; zigzag bands; broad or narrow bands which are transversal, oblique, or parallel to the veins; points, specks, spots in definite relations to veins or wing margin; systems of wavy lines, concentric lines (eyespot); areas without scales.

3. Within single families, *e.g.*, Sphingids, Papilionids, Arctiids, the majority of species show patterns that consist of numerous permutations of the same general plan of arrangement. (These plans have been worked out for different groups by Sueffert, Schwanwitsch, and Henke).

4. Patterns of very similar type may be different in regard to chemical or physical structure; the same element may be characterized in one species by chemical, in another by optical colors, etc.

These rather general facts already offer some points of attack for an analysis. As the pattern is generally composed of relatively few elements, differing in different species mostly in a quantitative way, it is to be supposed that the processes of pattern formation are also of a relatively simple type, which, however, permits of many permutations and quantitative shifts. Furthermore, since all patterns show definite spatial relations to the areas and general form of the organ (wing base, edge, etc.), the formation of pattern must be connected in some way with the

conditions within the wing as a unit. Other typical relations of the pattern to definite parts of the wing, such as the veins, are known, and these special structures also must be a part of what have been called the systemic conditions for pattern formation. Since a general plan of pattern is found in the different larger groups, different systemic conditions are supposed to be present in these groups. Finally, since similar or even identical patterns may be combined with different chemical or physical structures of an area—or, vice versa, the same chemical behavior over different areas—pattern formation and chemical specificity, *e.g.*, guanine, melanin, carotin, as pigments, must be caused by independent processes of determination.

To these general points of view two more special ones of general importance have been added.

5. Forms are known in which different generations (alternate spring-autumn or wet-dry seasons) exhibit different patterns, which sometimes, in tropical forms, may be so different that they can hardly be conceived of as simple quantitative shifts within a pattern; they actually show a different plan of pattern. External conditions acting upon the same genotype may then produce extraordinary changes of the type of pattern. (They can be produced also experimentally; see the classic case of *Vanessa levana-prorsa*). In view of what precedes, it may be inferred that the embryonic causation of such very different patterns may be due to relatively simple differences in the causative agents.

6. Cases are known of extreme polymorphism within a species, *e.g.*, the many different forms of females of *Papilio dardanus*, mimicking the patterns of very different families. In such cases, it is known that a few Mendelian genes are responsible for the entire array of patterns. It follows that extraordinary differences of pattern may be produced by the simple differences of reactions due to a mutant gene. In the same case, the different patterns are further controlled by sex; they are limited to one sex. The differences in development of the two sexes therefore may permit or prevent the realization of different types of pattern. This shows, again, that a relatively simple alternative may lead to far-reaching consequences regarding the pattern.

To this general review of the situation we may add a list—in no way complete—of known effects of mutant genes upon pattern in Lepidoptera:

1. The chemism of all areas of one type, *e.g.*, between the dark elements of pattern, is affected. The mutant gene acts at a level above the pattern, which is not changed. All mutants, mostly recessive, sometimes sex linked, changing a red-ground color to yellow or a yellow color to white are of this category. Examples: red and yellow *Callimorpha dominula* (Standfuss, 1890; Goldschmidt, 1924a); yellow and white *Colias* (Gerould, 1923); *Parasemia* (Standfuss, 1897).

2. Within the given pattern, all elements containing melanin pigment increase simultaneously and restrict the nonmelanic areas. These cases of melanism usually are of the polymorphic type, *i.e.*, typical quantitative steps from beginning to complete melanism are found and a series of additive (polymeric) genes are involved in the production of the different steps. Examples: Melanic polymorphism in *C. dominula* (Goldschmidt, 1924a); *Spilosoma lubricipeda*, (Federley, 1920; Goldschmidt, 1924a).

3. Within a given pattern, the whole pattern is intensified or bleached. Examples: *Abraxas grossulariata lacticolor* (Doncaster); *Argynnis paphia-valesina* (Goldschmidt and Fischer, 1922). In these cases, one sex-linked (*Abraxas*), *viz.*, one sex-controlled, gene (*Argynnis*) is involved.

4. Within the given pattern, individual elements, *e.g.*, the so-called *middle shadow* within the symmetry field, increase in regard to melanic scales.

Recessive or dominant genes may be involved and also sex-controlled behavior. If different genes controlling the same process but for different elements of the pattern are involved, combined and additive effects are produced by combination of these genes but in a different way from the foregoing group. Examples: *Lymantria monacha* (Goldschmidt, 1921b); flour moth (Kuehn and Henke, 1929-1936).

5. The whole unchanged pattern is overlaid by a melanic pigment. Here belong the frequent simple cases of recessive melanism, also of sex-controlled melanism. Example: many geometrids (T. W. H. Harrison, 1920). Here belong also the cases in which the pattern is unchanged but the whole tint of coloration is changed in degrees from light to dark melanins. Example: the male wings of geographic races of *Lymantria dispar* (Machida, 1924; Goldschmidt, 1933b). Here a series of multiple alleles is involved.

6. The basic pattern itself is affected by a shift of the relative distance (or size) of the elements. Example: enlargement or restriction of the field of symmetry in the flour moth (Kuehn and Henke, 1929-1936). A dominant mutation is involved here.

7. The basic pattern is affected by suppression of some of its elements. Example: the recessive mutant *lunata* of *L. dispar*, (Goldschmidt, 1927*c*, 1933*b*) showing no zigzag bands in the system of symmetry.

8. The whole basic pattern is changed into a quite different pattern. (Examples: mimetic *Papilios*, De Meijere, Fryer, Poulton, and collaborators; see Ford, 1936), where the process is sex controlled and dependent upon a few recessive genes and their recombination.

These are the types of genetic facts, which are to be correlated with the embryological facts in order to gain a general insight into the all-important problem of the production of pattern by the action of genes. It may be added that a large bulk of similar genetic evidence could be cited regarding the control of pattern by mutant genes in the caterpillars of *Bombyx* and *Lymantria* (Toyama, 1906*a*; Tanaka 1913, 1916; Goldschmidt, 1921*b*, 1928*b*); in the larvae and imagoes of chrysomelid beetles (Tower, 1906; Tenenbaum *et al.*, 1933). But in all these cases, the additional experimental and embryological knowledge are missing.

There is little difficulty in explaining all these cases in which genes control differences within the pattern (change from red to yellow, melanism overlaying pattern). The action of the mutant gene is of the same type as has been described. It does not involve the problem of pattern itself. Goldschmidt (1927*c*) worked out a theory designed to reduce this problem to the already known principles regarding action of the genes. His interpretation may be stated in general terms thus: The genes controlling pattern act by producing definite reactions of definite velocity. These are properly timed; *i.e.*, their time elements are arranged so that the thresholds of effect are reached in a definite order, thus insuring for each process a definite situation upon which to act. In the known cases where there is genic control of the velocity of differentiation in different areas of the pattern, at a given moment two such areas are found in a different stage of development. If, now, another gene-controlled reaction leads to the production of, say, guanin, to be deposited in the

scales, only those scales can be impregnated with it which are in the proper stage. This means that the substance in question is deposited only in definite areas. (See the facts of scale development, page 241.) This one model serves for the description of many other types of patterning in similar terms, using velocities, thresholds, time of onset or end of action, and similar processes of simple quantitative behavior as elements. This has been worked out in Goldschmidt's book (1927c).

But the decisive point remains: This or any other explanation requires that a primary stratification occurs at a definite time leading to areas of different constitution. Only then can begin the automatic action of a system, as the one described.¹ These primary areas in our case were the areas of different speeds of differentiation (caused primarily, so it seems, by different rates of cell division, see page 244). Goldschmidt assumed that this process occurs as a consequence of the production of a substance at a definite time, which acts upon the substratum, *i.e.*, the young wing, like the evocator substance in the formation of Liesegang rings within a colloidal medium. This means that the genes responsible for this primary pattern or stratification act just as all genes do, producing a definite substance at a definite time; but that "the conditions of the system," *i.e.*, the physicochemical structure of the *Anlage* and the laws of chemical equilibrium, cause a reaction with this evocator substance which leads to an automatic distribution of the products of reaction in a definite arrangement or pattern, after the model of the formation of Liesegang rings (see discussion, page 205). On the assumption that the whole wing acts as a unit, there was no possibility of making more specific assumptions regarding this phenomenon of stratification as applied to the pattern of the butterfly wing. The work of Henke and Kuehn (1929-1936) has led one step further. They showed that in the formation of the primary pattern, the following processes take part.

1. An already present general subdivision of the wing area into different fields, which are, however, not yet determined in their later extent. In the terms that we used, this would mean that there is not one single process of evocation for the whole wing but a number of centers from which this process starts. (These

¹ This is, of course, the same situation that was discussed repeatedly in regard to embryonic pattern.

are the outlets as designated in Goldschmidt's earlier work.) It would also mean that the Liesegang-ring model would probably not apply to this part of the problem.

2. For at least one of these fields it was proved (as reported above) that its limits, the later system of symmetrical bands, are formed at the edges of a determination stream which flows with known speed across the wing in a definite bed (see Fig. 38) and at a definite time. Here, then, we actually see the process of stratification, caused by a spread of evocator substances from different points of outlet and causing the deposition of some product of reaction (here a substance retarding differentiation or producing mitosis) where the stream comes to a standstill (or meets the neighboring field). The decisive points of Goldschmidt's interpretation have thus not only been found to be correct, but they have, in addition, been put on a safe experimental basis. This important step taken by Henke and Kuehn permits the following application of general ideas about genic action to further detail of pattern formation (to be found partly in Goldschmidt's first discussion, 1920*b*). A number of quantitative variables are added to the system, which can account for many details of pattern formation by simple quantitative shifts in one or another direction. These are the relative time of opening of the "outlets" of the determination stream into different fields (see the different sensitive periods); the relative velocity of spread of the determination stream as determined by its own composition and the physical nature of the substratum; the relative amount of substance available as a determination stream; the amount of reaction product and the locus where it is formed or accumulated. Needless to say, mutant genes are those which act by quantitatively changing one of these variables.

Some of these have actually been analyzed by Kuehn and Henke in the mutants and phenocopies of the flour moth. The results of temperature action in the sensitive period in different lines were compared with the results of operation upon the wing. Some of the details that have not been mentioned thus far are the following. In a pupa of 72 to 84 hr. of age, the determination of the pattern has been completed, resulting in the described process of increase of number of mitoses in the later dark areas. Two periods are distinguishable within the first 3 days of pupal life

(at 18°C.). In the first, a temperature shock enlarges the symmetry field; the operation shows that the determination is not yet finished and that the stream is in progress. In the second half of the 3-day period, temperature shock produces narrowing of the field in question. The operations (destruction of parts of the field) produce the same effect and show in 48 to 60 hr. old pupae the determination stream in flow, as reported. It starts from both wing margins, joins in the center and then spreads toward wing base and tip. A stopping of this flow means a smaller field. One of the mutant genes *Sy* stops this process of spreading before it is finished. Certain steps of this spreading process are more frequently realized in the different experiments, which might indicate areas of special resistance to the spreading (or a wavelike process of spreading, Goldschmidt); one such line coincides with the limits of the fields produced by the gene *Sy*. There is another gene *Syb*, which broadens the field of symmetry; this might also be done by temperature shock. The two effects cannot be added (see the different behavior of the vestigial case, page 22), and therefore the authors assume a line of absolute resistance in the substratum. Here, then, have been analyzed two phases that might influence the pattern by quantitative variations and their mutual interplay: (1) what the authors call the impetus of spreading, which is the same as the quantity of determining substance in Goldschmidt's old interpretation; (2) the resistance to spreading, which in Goldschmidt's terminology was the conditions of the system. Since it is found that operations upon *Sy*-animals more frequently fit one definite stage of the spreading of the determination stream, as compared with the same operations upon Wild type, it is specifically concluded that the gene *Sy* does not affect the stream but the resistance of the substratum, preferably at a definite time. These and similar facts then demonstrate clearly the presence of a system of such a type as had been postulated by Goldschmidt in his first attacks upon the problem.

As all these details are rather complicated, we might finally give a short picture of the origin of any more complicated type of wing pattern, adding that each of the steps may be controlled by mutant genes, which shift the process in question quantitatively in time of onset, duration of action, locus of action, quantity of reaction product, and threshold of action. The first pattern

to be laid down very early in development and not yet analyzed genetically or embryologically is the pattern of wing shape and distribution of wing veins. This primary pattern is of very early origin (Goldschmidt, 1920*d*, drew attention to the fact that the pattern of wing veins is already visible on the chitin of the pupa before these veins have been formed); and it fixes the systemic conditions for the later processes, resistances, drains, etc., as previously described. The second pattern is the pattern of future fields or areas determined by the location of the points of outlet of a determination stream or field centers. Extreme cases, such as the case of *Papilio dardanus*, show that this pattern is controlled and may be shifted by mutant genes (also sex differences) considerably. The genetic facts point out that very simple events, like shifts of a process in regard to time, may be involved in such changes, but nothing is known yet as to how these points are determined primarily. There is a suspicion that they may coincide with growth centers. The third patterning process, described below, controls the limits of these areas or fields and the type of pattern of visible field limits (bands, etc.). This process is the formation of a determination stream proceeding from these outlets with definite velocity and in a bed set by the foregoing patterning processes (systemic conditions). Time of onset and length of flow of this stream, together with corresponding states in the neighboring areas, and the systemic conditions, determine the detail. Mutant genes are known to change these processes, also temperature effects. The fourth step found is the production of differential cell divisions at the edge of the stream, which thus appears to be of the type of a growth substance. Differential mitotic patterns again lead to an earlier start of the phase of scale differentiation outside the edges of the stream, *i.e.*, later cell differentiation at the edges, the bands. The latter cell groups are those which will receive pigment by being in the proper condition for its colloidal solution, when another process supplies the chromogen. This pattern, again, may be overlaid by a new gene-controlled process which furnishes more or less melanin, or different-colored substances, to all or any fields that are in a condition to receive them. Again, mutant genes control these productions.

c. Additional Facts.—In order clearly to present those facts which have pushed the analysis to the point where it stands

today, we have repeatedly passed over points that would have required more consideration. We propose to discuss these now in the form of additions.

The decisive point, the analysis of which is still more or less in the theoretical stage, is the formation of those primary patterns which have been described as the distribution of the field centers or points of outlet. This problem is, of course, identical with the problem of embryonic stratification, as mentioned before. We have often used the comparison with the production of Liesegang rings in colloidal solutions after introduction of some chemical, acting as an evocator. Gebhardt (1912) was the first to draw attention to the great similarity of some patterns on butterfly wings with Liesegang rings, and he believed that pigment deposition in the scales was actually such a process. Kuester (1913) applied this same principle to numerous rhythmical structures in plants. In its original form, the idea had to be discarded as applied to the butterfly wing, when it became known that the pattern was determined independently of pigment formation (Goldschmidt, 1920*d*), though it was still possible to make use of the same idea in explaining the arrangement of different determining stuffs (growth substances) in the form of a rhythmic pattern or stratification. As we have seen, this is probably not the case for the primary patterns of the butterfly wing, though certain secondary patterns within the fields or spreading over the whole wing may be explained thus. (Similarly with many rhythmic developmental patterns, like segmentation.) A few additional facts regarding this phenomenon may therefore be mentioned. In detail, it may be produced by different processes. A substance present in the system may spread by diffusion and be arranged in a rhythmic way; or the phases of the rhythm may be produced only as a reaction *in loco*; or a precipitate may be formed in a rhythmic procession. We may assume that one or the other of these phenomena occurs when rhythmical patterns are involved, and we may accept this as a general model for developmental, simultaneous stratification in cases where no other related process of diffusion is known. Thus far, no actual genetic or experimental fact is known to show a Liesegang phenomenon at work, though some patterns apparently require it. Quite recently, however, Becker (1937) showed that a special pattern formed upon the tergites

of wasp queens, independent of the typical pattern of wasps, is the product of a Liesegang ring formation with mechanical evocation.

There are rhythmical patterns which suggest at first sight a Liesegang phenomenon. Henke (see 1935) calls them simultaneous rhythms and points out that they are characterized by the absence of a center of diffusion and therefore must have a different origin. Here belong the tiger and zebra stripes and their like. Henke points to the fact that tiger and lion hybrids exhibit a pattern that is a kind of compromise between the stripes of a tiger and the rosettes of a young lion, which shows that the different genes of these species control the same general process. Many authors have tried to find an explanation for such patterns. Haecker was the first to assume that rhythmic growth of the skin was responsible, in so far as pigment would be deposited in zones of intensive growth. This, of course, would refer the problem to the formation of a primary growth pattern. Goldschmidt (1920c) for some time accepted this solution but was later led to a different formulation when he had seen that a young tiger embryo exhibited the whole later pattern in form of epithelial papillae, which represented the *Anlagen* of the large hair (*Leithaare*). This same fact was found and elaborated by Toldt (1912) in a series of papers. This pointed to a primary pattern formation in relation to the arrangement of hair follicles. Krieg (1922), who returned to this subject, thinks of tensions within the skin at the time of pattern determination (= distribution of something) which makes the determining stuffs collect in definite lines. This makes it possible, of course, by adding the rate concept, to explain different patterns by different times of onset of the action of determining stuffs. This view, indeed, accounts well for the facts and has the advantage of permitting tests in forms like dogs, cats, and cattle, where these patterns are controlled by mutant genes, and other patterns by other mutant genes. Such an analysis is still missing. Growth tensions, of course, would then adequately explain a primary, general, and simultaneous pattern, not showing any centers of origin. As such tensions would be the automatic result of former developmental processes, another type of automatic patterning could be added to those already discussed. Henke (1935) points out that many elementary processes of pattern formation might come into this

category, *e.g.*, the arrangement of hair, feathers, glands, etc., in the skin.

In studying the wing pattern of Lepidoptera, we had to point out the existence of primarily determined centers (outlets) for the determination process, the centers thus dividing the surface of the organ into fields. The same problem occurs again in the piebald patterns of mammals (also fishes). Goldschmidt (1920*b*) pointed out that there the same two phenomena are involved as in the moth wing, *viz.*, the inherited pattern of outlets (field centers) and the control of quantity, berth, time of flow, etc., of the spreading substance responsible for pigmentation. Kuehn (1926) and Henke (1933*a*) have shown that the fields thus created are rather independent of each other; *e.g.*, *A* may be black, and *B* white, or vice versa; in *A*, very little pigment may have "flown out" from the centers; in *B*, none; and in *C*, the whole field may be covered. This points to a process with a time element, which Goldschmidt (1920*c*) had termed the order of opening of the outlets. Genetic work with such patterns shows that mutant genes exist, controlling the quantity of released pigment, frequently in an additive way in series of multiple allelomorphs; further, genes controlling the arrangement of the centers and their symmetry; also, genes controlling what we called the order of opening of the outlets, resulting in special features for each field; and, of course, also the genes controlling the color of pigments (see the numerous papers on spotting in mice, rabbits, rats, guinea pigs, horses, dogs, by Castle, Wright, Dunn, Phillips, Ibsen, and others). The material already existing in these groups might profitably be used for a deeper analysis of this type of pattern, an analysis that has not yet been made from the standpoint of physiological genetics. Attention may be called to Iljin's study (1926) of piebald patterns in guinea pigs. He assumes that centers of pigmentation (the *outlets*) are not found, but centers of depigmentation, *i.e.*, the negative picture. This leaves, however, the problem of gene-controlled pattern where it was. The facts reported above (page 155) regarding Himalayan rabbits and Siamese cats, demonstrating an interesting interaction between gene products and environment, ought also to be kept in mind, because internal conditions might assume the role of environment and superimpose a pattern effect upon a nonpatterned gene effect.

A beginning of such an analysis has been made for a similar object, the feather areas (pterylae) of birds, which certainly again present areas with a center of outlet of feather-determining stuff. Within such an area, according to Holmes (1935), first a row of follicles are formed simultaneously; from here the process spreads laterally and medially as well as anteriorly and posteriorly and might therefore be described as a determination stream. Within such a field, certain regularities have been found by Juhn and Fraps (1934); Juhn, Faulkner, and Gustavson (1931); and Fraps and Juhn (1936). The feathers on both sides of the first row may behave as mirror images in regard to structure and color; their rates of growth and length of regenerated shaft have a definite size increasing in an anterior-posterior direction. Fraps and Juhn showed a similar relation for barb length in regeneration relative to the distance of the feather from the central row and were able to describe this in terms of field functions (which is only a description in mathematical terminology for the same things which we treated thus far as spread of stuffs). These pterylae coincide partly with areas of pigmentation (Juhn), and possibly the same processes are involved in their formation. Since here, again, mutant genes are known controlling the different features of the pattern, we may expect more information from this material.

Another attack upon this problem has been made by Goodrich (1933), in fishes. We have referred to his work on *Oryzias* where he could show that black and yellow melanophores are involved. In yellow fish, the melanophores are present but not able to form pigment. As the Dopa reaction shows, the oxidase is not lacking, but the chromogen which is produced by the action of the dominant gene. The difference between the two alleles is thus one of quantity of effect. This effect takes place in the individual cells; it is cell localized. As these chromatophores migrate in the embryo from a center of origin, their determination in regard to chromogen formation occurs probably in this early stage. There is also a variegated type which requires that in the early stage a pattern has already been formed of cells with different powers of chromogen formation. But this pattern could just as well be determined later by local conditions. No experiments of the type of Twitty's (see page 179) have yet been performed to answer this question.

A real pattern process is involved in the goldfish (*Carassius auratus*). Here black and yellow chromatophores are present, and the mottled patterns are caused by a secondary destruction of pigment cells in definite areas (Berndt, 1925; Fukui, 1927, 1930). The resulting type depends upon the time of beginning of destruction, place and amount of destruction, and whether or not also yellow chromatophores are finally destroyed. Thus a seriation brown self—variegated black and orange—orange—variegated orange and white—white may be obtained. The pattern itself is quite irregular and is complicated by the presence of a pattern of scales with and without (transparent-type) guanine crystals. There is, according to Fukui, a relation between the pattern of chromatophore destruction and the structure of the skin, and the destruction of pigment is combined with phagocytic action. Goodrich and Hansen (1931), who made a quantitative study of these facts, point out that most of them may be explained by a system of reactions, producing the destructive agent with definite velocities. In this respect, we may compare the case to the case of destruction of the vestigial wing. But here, as there, remains the problem of pattern. In the *vg*-case, it was obviously a consequence of the structure of the wing, prescribing the bed of spread of the lytic substance. In the goldfish, the pattern seems to be imposed by the distribution of lymph spaces from which the lytic action starts, a theory actually assumed by Fukui. Goodrich points out that the pattern in *Oryzias* and in *Carassius* is to be explained on a different basis. There is no doubt that the latter is of the type resulting from the interaction of a gene-controlled process (production of the lytic substance) with what we termed the conditions of the system. (We might apply the terminology used before and speak also of the arrangement of the outlets for the lytic stuff.) The principles obviously are always the same, though the details may be very different. In the case of *Oryzias*, we do not know the patterning agent, but no doubt it will fall into one of the known categories. It may be added finally that experiments in transplantation of scales (Goodrich and Nichols, 1933) show that the lytic action is limited to definite times in development, as expected.

In other fish species, more complicated patterns appear. In *Platypharodon*, for example, Gordon and Fraser (1931) have traced

a number of pattern elements to individual genes. As these patterns may be combined in a single individual, just as such wing patterns in *Drosophila* as miniature, beadex, expanded may be combined in one wing, each element must be caused by an independent embryological process. Therefore, in these and similar cases (Lebistes, Winge), an analysis will have to be applied of the type used for the wing of the flour moth. No facts are yet known to warrant more specific conclusions.

We may finally give the list of types of pattern formation as compiled recently by Henke (1936), adding such information as is pertinent to our topic:

1. Patterns based on chimeric development. These are the patterns in gynandromorphs, chimeras, somatic mutations. They throw light on problems of autonomous differentiation but hardly on actual developmental patterns.

2. Patterns based on rhythms in time. Here belong the patterns of feathers, produced by hormone injection. Possibly also patterns like feather pattern in Plymouth Rock. Their relation to genic action is not yet clear.

3. Crack patterns. These have not yet been mentioned. Regular cracks, as in a shellac film or *craquelé china*, have been used by Hirata (1935) to explain regular patterns in beans. If we substitute zones of different growth or tension for the cracks, the consequences will be the same as for the latter pattern-forming processes.

4. Areas of diffusion from one center. Here belong the cases of spotting, pterylae and their like.

5. Field limits as pattern. Here belong the best analyzed cases of the bands on the lepidopteran wing, determined by the front of a determination stream. They are combined with a pattern of differential velocity of differentiation.

6. Rhythmic diffusion from centers. This is the Liesegang ring type of pattern-forming process.

7. Simultaneous rhythms. An instantaneous rhythmical arrangement, e.g., by tensions in a membrane, producing zebra-like patterns.

8. Combination patterns. This is the Lepidopteran type of pattern, composed of different areas with a combination of some of the foregoing pattern-forming processes.

9. Pattern by differential growth. This is not contained in Henke's review, because not involved in color pattern, but most important for embryological pattern formation. All of the foregoing types may combine in the embryonic patterning, though some of them may be more frequent, *viz.*, 4, 5, 6, 9.

There can be no doubt that the formation of patterns, *i.e.*, the decisive process of development, may, even in the present stage of our knowledge, be reduced to the action of a gene-controlled system of properly timed reaction velocities. These reactions set in motion the different types of stratification processes discussed and simultaneously provide the details by proper distribution of onset, length of action, and threshold of all the other incidental processes. A simple event at a definite time and place will automatically set in action the whole series of consecutive events. But each partial event may be shifted by mutant genes or the action of modifiers or the environment. There is no reason to believe that other developmental patterns are controlled in a different way from those which have been used as models.

III. THE CYTOPLASM AND THE ACTIVATION OF THE GENE

In our discussion of the facts and interpretations of physiological genetics, we were concerned mainly with the action of the genes, situated within the chromosomes of the nucleus. We took for granted that the seat of the reactions controlled by the genes is the cytoplasm, both the cytoplasm of the individual cells and the cytoplasm of a group of cells taken together as a unity (a field or territory in the sense of experimental embryology). The role of cytoplasmic differentiation in development and determination has been discussed in connection with the phenomena of stratification, primary chemodifferentiation, and different types of induction. In all these cases, the cytoplasm was considered to be the substratum upon which the genes work, though the processes happening within the cytoplasm may take their independent course once started by the action of the genes. In this chapter, we have to consider the facts that may lead to a better understanding of the part assigned to the cytoplasm in heredity.

The questions that will have to be answered are:

1. If the cytoplasm is the substratum upon which the genes are acting, is it possible to formulate more specific ideas of this interaction?

2. At the outset of such an interaction, which must be of an orderly sequence, a process is supposed to occur that may be called the activation of the gene. What does this mean?

3. Is the activity of the cytoplasm in conditioning orderly development always steered by the genes, or is an independent activity of the cytoplasm known?

4. If the cytoplasm has independent genetic properties, are these of the same type as the properties controlled by genic action, or are they of a different, possibly more generalized, type?

1. INTERACTION OF NUCLEUS AND CYTOPLASM

The first question, regarding the type of interaction of genes and cytoplasm, is difficult to answer, because only very indirect

evidence is available. In a general way, a number of possibilities are given. There is, first, the following alternative: Either the genic action, whatever it is, takes place within the resting nucleus, or it is confined to the mitotic stage, when chromosomes and cytoplasm are in direct contact. In favor of the latter possibility, the facts may be mentioned regarding the relation of mitotic divisions to determinative processes (see page 244). But these facts may also be interpreted differently. In favor of the first alternative, the behavior of egg cells of the determinative type may be mentioned. In such cells, decisive developmental processes, the chemodifferentiation, occur in the resting nuclei.¹ Still a third possibility might connect the two alternatives, *viz.*, that the products of genic action are formed within the nucleus but set free only when the nuclear membrane disappears. It is known that at least in some eggs determinative processes are started with the bursting of the germinal vesicle.

Goldschmidt (1927*c*) and Koltzoff (1935*a*) have suggested a connection between this phenomenon and the liberation of gene-controlled substances formed during the growth period of the nucleus. In a way, such views go back even to the discussions upon the meaning of the nuclear and chromosomal behavior in the auxocyte, centering around the terms idiochromatin and trophochromatin (see Rueckert, 1899; Goldschmidt, 1904). In a general way, it may then be assumed that the interaction of genes and cytoplasm occurs through the nuclear membrane, though other possibilities cannot be denied. This might mean either of two things: (1) The direct products of genic action diffuse through the nuclear membrane. As these products are probably in the nature of catalyzers, either only low-molecular catalyzers are involved, or the nuclear membrane must be permeable for large molecules. (2) Substances from the cytoplasm enter the nucleus, and only the products of catalysis return into the cytoplasm. There are only very few facts available on which to base inferences. Most suggestive are the strange and complicated intranuclear processes which occur in the growing oocytes of *Selachia* and *Amphibia* and which demonstrate an immense activity of the chromosomes, connected

¹ Quite recently Stern (*Nature*, Oct. 30, 1937) has drawn attention to the fact that genic actions are known which occur within single cells during the resting stage of the nucleus.

with the elaboration of manifold substances, having to do obviously with the growth and probably also with the chemodifferentiation of the cytoplasm. A direct demonstration of the relations is available only in the experiments of Haemmerling (page 192), which show that the intact nucleus controls the production of formative substances, showing a gradient away from the nucleus. But we do not know how and where they or their precursors are elaborated under the control of the nucleus. Thus we must be content to know that certain decisive cytoplasmic activities and differentiations are controlled by the nucleus, *i.e.*, by the genes, without being able yet to follow chemically the details of these interrelations. (A theory to account for the facts of development in rather the opposite way from the one usually assumed by geneticists has been published recently by Just, 1936).

It may be added that Koltzoff (1935) thinks that some substances that are difficult to synthesize are actually identical with genes, which produce their like by assimilation and give off the surplus into the cytoplasm. Davenport (1935) thinks that the genes lie near the surface of the nucleus. They attract cytoplasmic molecules with the opposite charge. The residual charge suffices to attract another molecule to the second, resulting in making the two cytoplasmic molecules independent of the gene-molecule, which starts the same process over again. It must be honestly said that thus far this problem has not found any factual or theoretical solution.

2. THE ACTIVATION OF THE GENES

The second question concerns the activation of the genes. If genes control definite cytoplasmic processes occurring at definite times in development, *e.g.*, the production and flow of the organizer substance in amphibian development, they are supposed to be activated at the proper moment to set in motion the cytoplasmic process. We have already reported the many facts that demonstrate the time of onset of genic action in different cases, ranging from the very end of differentiation down to the behavior of the first segmentation spindle. In order to form a general idea of these processes of activation, we may describe them as follows. Whether the genes are catalyzers or not, the decisive immediate product of their action must be

catalyzers. As enzymes are extremely specific, their action requires the proper substratum; to which might be added the optimum conditions in acidity, in regard to coferments, in the relations of enzyme and carrier substance, in colloidal and viscosity conditions of the medium. When all these conditions are properly provided, the action of the enzyme (which might always have been present since fertilization, though perhaps not in sufficient concentration) may begin, and this we call now the

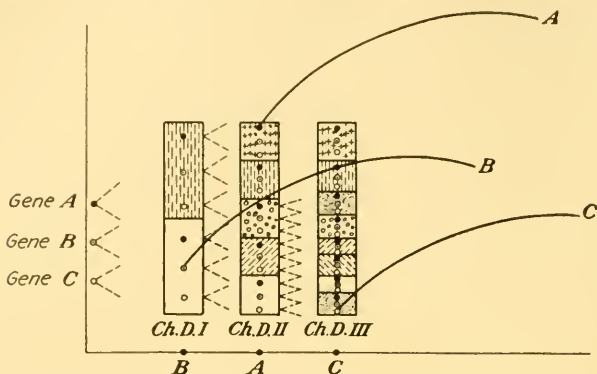


FIG. 54.—Diagrammatic representation of the activation of the gene by proper cytoplasm. (From Goldschmidt, 1927, *Phys. Ther. d. Vererb.*)

activation of the gene. It was shown in the chapter on developmental mechanics that development, from the standpoint of the whole embryo, *i.e.*, the cytoplasm, consists in a series of "stratifications" of cytoplasmic differences initiated by a gene-controlled process. Thus, one substratum is transformed into two or more different ones, which now can provide the proper substratum for the action of new genes. We may thus describe the activation of the genes in terms of the accompanying diagram (Fig. 54). We assume three genes A, B, C which, or the products of which, are ready for action as soon as the proper substratum is provided. At a stage of development, Ch. DI, a cytoplasmic segregation into two different substrata occurs. The lower one is the proper basis for the action of gene B, and the chain of reactions controlled by this gene is set in motion. At the stage Ch. DII, the stratification has produced five areas, the topmost of which is the proper substratum for the gene A. The third stratification provides the substratum for C. The actual facts may be much more complicated, but it is most probable that the general relations

between genic action and cytoplasmic component are of this type. It has to be added that the situation might be obscured if genic action had produced the pattern of stratification already before fertilization. In this case, only the maternal genes would have taken part in the process, which thus may appear as an independent cytoplasmic action. This situation was discussed on page 206.

3. CYTOPLASMIC HEREDITY

The third problem is the one usually meant when the role of the cytoplasm in heredity is discussed. Is the protoplasm not only the substratum for the action of the genes but also an independent part of the germ plasm, directly influencing the hereditary traits by action of its own?

A. MEROGONY

It is known that some of the classic work in experimental embryology was directed to a solution of this problem (Boveri, Godlevski). In the experiments on merogony (purely paternal nucleus in the cytoplasm of another species), first a positive result was obtained, but this was later discarded by Boveri himself as due to misinterpretation. In recent years, these experiments have been revived with partly different methods. Using the same method as Boveri, Hoerstadius (1936) produced hybrid merogons between two species of sea urchins which could be raised to the pluteus stage. The skeleton turned out to be not typical. The club-shaped ends of the main calcareous rods characteristic for one of the species (*Psammechinus*) are determined by the nucleus. They are intermediate in the hybrid and typical in merogons with *Ps.* nucleus. In merogons with *Ps.* plasma, abnormal rods appear; Hoerstadius, however, seems to believe that this does not mean a plasmatic determination but only an abnormality produced by the nuclear action in foreign cytoplasm.

The second method applied to such studies is the production of germinal layer chimeras (von Ubisch, 1936; Hoerstadius, 1936) in echinoderms by transplanting the micromeres of one species into the blastula of another. In these cases, combination skeletons may be formed which look very much like a hybrid

skeleton. No influence of the cytoplasm could be found, though it would be difficult to prove it.

The third method has been introduced by Baltzer (1933) on the basis of old observations by Spemann, producing merogons in *Triturus*. The *Triturus* merogons did not grow long enough, however, to permit an analysis of the specific differences. Later, it was shown that merogonic tissues, if transplanted to a normal host, may survive and develop far beyond the stage possible in the pure merogon. This fact has been used recently by Hadorn (1936) to perform an experiment of the type discussed here. The egg of *T. palmatus* is fertilized by sperm of *T. cristatus*, and then the female nucleus is removed with a pipette. After gastrulation, a piece of presumptive epidermis is removed and transplanted to a gastrula of *T. alpestris*. The merogonic epidermis will cover most of the left side of the resulting chimera. This can be bred beyond metamorphosis. The skin of *T. palmatus* which furnished the plasma of the merogon is characterized by papillae made up of a series of flat cells. The epidermis of the part of the chimera derived from the merogon shows exactly this structure, *i.e.*, the structure of the species that furnished only the cytoplasm of the merogon. It must be added, however, that the alpestris host produces the same structure. It is therefore possible that the effect has not been produced by the cytoplasm of palmatus but by an induction from the alpestris host, which, however, would be a quite unusual feature (though existing in *Acetabularia*). In any case, the experiment is not convincing enough to derive conclusions upon cytoplasmic inheritance. Very little is known of merogony in plants. East (1934) cites a few cases obtained more or less fortuitously after crossing by Kostoff (1929), Clausen and Goodspeed (1925), Clausen and Lammertz (1929), and Nawaschin (1927), none showing any cytoplasmic influence.

A second somewhat similar type of experimentation in this field has been performed on cells of fungi by Harder (1927). In Basidiomycetes, a stage occurs after conjugation in which one of the cells contains a mixture of the protoplasm of both parents but only one nucleus. This cell may be isolated and grown. If the two parents belonged to different forms (*Schizophyllum commune* and *Pholiota mutabilis*), the influence of the mixed protoplasm as contrasted to the one nucleus could be studied. Some of the hereditary traits showed only the influence of the

nucleus; but others, noticeably the growth habit, showed a cytoplasmic influence. This experiment ought to be repeated with the necessary variations to make sure that actually a cytoplasmic effect was involved. It seems probable that it was, in view of the work soon to be reported.

B. PLASTIDS

In all these cases, only the general effects of nucleus and cytoplasm were approached by the type of experimentation, without a possibility of isolating the action of individual genes in different protoplasm.

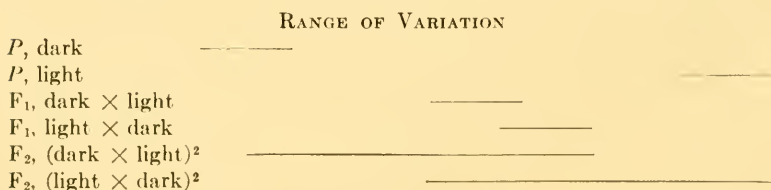
Now genetic literature is overflowing with analyses of reciprocal crosses in which the nuclei are alike in regard to individual genes, whereas the protoplasm is different according to the mother. In the overwhelming majority of cases in which the crosses are made between the wild form and its mutations or mutations *inter se*, no influence of the plasmatic constitution upon the result becomes visible. Reciprocal crosses and their offspring behave alike, of course, with the exception of differences in the X- or Y-chromosomes. We exclude also such differences as find on closer inspection a special explanation. There are, for example, the cases of plastid characters in plants, first studied by Correns, which show inheritance through the mother, as usually no plastids are transmitted by the pollen tube.

We do not intend to go into the details of the plastid problem here, as we are concerned only with the problem of cytoplasmic heredity. Among the cases studied by Correns (1928) are those in which he came to the conclusion that plastids are prevented from becoming green when situated in a definite cytoplasm, called by him a diseased cytoplasm. But such cases might also find a different explanation. Renner had shown (1924) that a normal behavior of plastids may depend upon definite genetic constitution, as, in *Oenothera* crosses, plastids within their own cytoplasm will not form chlorophyll in the presence of foreign chromosomes. Following up this work, he came recently (1936) to the conclusion that in all the manifold facts concerning plastid inheritance and behavior, including differences in reciprocal crosses, no cytoplasmic effect is involved. His opinion is that plastids are independent hereditary units which might even show changes comparable to mutations. The facts of all the different types of

panachure are attributed thus exclusively to the constant properties of the plastids themselves. If Renner's views prove to be correct, the facts regarding plastid inheritance will be ruled out of the problem of cytoplasmic action.

C. CYTOPLASMIC INFLUENCE UPON GENE-CONTROLLED CHARACTERS

It is very significant that though no cytoplasmic influence upon the action of genes in controlling visible characters has been found, when simple mutants were involved in the cross—one exception will be mentioned later—quite a number of cases with positive results are available that are all alike in that the systematic distance between the parents is rather large. If we omit at present the matroclinous species crosses which always have been suspected of being caused by cytoplasmic differences of the parents, the first properly analyzed case was found by Goldschmidt (1924*b*). The Mendelian characters in question were differences between subspecies or geographic races of *Lymantria dispar*, viz., amounts of pigmentation in the caterpillars of different races. The type of heredity found may be indicated by the following diagram which applies to practically all other cases.



This means that F₁ is matroclinous and that in F₂ a 1:2:1 segregation takes place, the range of which, however, is shifted in the reciprocal F₂ toward the maternal side. A corresponding effect was obtained also in backcrosses. The conclusion, then, was that it is not irrelevant for the action of the genes on which or within which cytoplasm they are acting. Within the two races, the respective phenotype was the result of the action of the genes, given the specific cytoplasm. If the same genes, however, were working within a different cytoplasm, the result of their action was shifted toward the type to which the cytoplasm belongs. Light genes in dark cytoplasm—to use these brief

designations—produce also in extracted homozygous condition a phenotype that is darker than the pure light race, and, vice versa, dark genes in light protoplasm fail to produce the completely dark forms among the homozygous segregants. When the same experiments were performed with different races distinguished by the presence of less and less light allelomorphs of the same dark gene, the same result was obtained but in a lesser degree. There can be no doubt that the geographic races in question were different in regard to some element of their plasmatic constitution. Since that time, other quantitative, gene-controlled characters in the same material were found to behave exactly in the same way, *e.g.*, length of hibernation and velocity of larval development (see review in Goldschmidt, 1934*b*).

In recent years, a number of observations of a similar type of inheritance have been made, and with attention drawn to this problem more cases will be available. I mention only the report by Murray and Little (1935*b*) who found that hereditary tumor incidence in mice, studied in reciprocal F_1 and F_2 , behaves exactly as the case just reported, thus showing an influence of the cytoplasmic condition.

In this piece of work, however, one important check was missing, *viz.*, the analysis of the extracted homozygotes in further generations, which could not be made for technical reasons. But similar work has been done since with similar results and the additional filling of the just-mentioned gap, at least in part. We shall soon see, however, that a decisive point is thus far not settled. Of first importance in this connection is Wettstein's (1924–1934) work with mosses. In this material, crosses between races, species, genera, and even subfamilies are possible, whatever this may mean among bryologists. Generally speaking, the crosses between races of one species were reciprocally alike and did not show any influence of the cytoplasm upon the gene-controlled characters. All other combinations, however, showed such an influence, increasing with the taxonomic distance. Among the characters studied, some, like the form of leaves, showed very clearly the plasmatic influence after the manner that we have just discussed for the *Lymantria* case; others showed it as less pronounced or not at all. In the case of the leaf character, it was possible in the species cross to obtain a further back-

cross generation which behaved according to the expectation derived from the given explanation. In the generic cross, no such direct way of testing was possible on account of the sterility. But it was to be expected that among those spores which are normally formed, because the respective gene recombinations are viable, no difference of viability would exist between gene recombinations of predominantly paternal or maternal origin. As a matter of fact, more maternal recombinations were found in the reciprocal crosses, and this is interpreted as meaning that the genes work more successfully with the cytoplasm of their own species. In this cross, it was also possible to backcross over again in succeeding generations with the paternal species, but the result was always maternal offspring, which shows that the supposed plasmatic incompatibility with the foreign chromosomes has not been changed. Unfortunately, also, in this case the decisive experiment with extracted homozygotes in reciprocally different cytoplasm could not be performed, except for one generation of a backcross on one side only (see page 275).

The plasmatic influence that was found in these more complicated crosses was tested in many different ways by Wettstein and his students (Doerries-Rueger, 1929; Becker, 1931; Melchers, 1935) and was found to apply to many individual characters like osmotic pressure and division rate. All these cases may, however, be interpreted as a general action of the cytoplasm upon gene-controlled reactions. No influence has been found that could properly be called a cytoplasmic determination of a definite trait.

One more case of a similar type in plants might be mentioned, because it shows again certain of the general features that we have met thus far. Sirks (1931*a, b, c*) found in his crosses with beans no reciprocal difference of crosses within the two sections of *vicia faba* called major and minor. But in crosses between these sections, differences came to light that have to be regarded as of plasmatic nature. If a certain linkage group of genes is represented in a cross, the homozygous forms appear only in F_2 if the genes in question are situated in the protoplasm of the form from which they entered the cross. Otherwise, they are not viable. In other words, the protoplasm of the major group is lethal for a certain chromosome derived in homozygous form from a minor plant. Or, stated another way, the chromosome

in question contains either a lethal gene or is as a whole lethal, the gene acting only in major cytoplasm in a homozygous state. A case studied by Honing in *Canna* subspecies crosses is similar but less extreme in plasmatic effect; others found by Skalinska and Gairdner fall in line. In addition to this case, still more cases were found that resemble our *Lymantria* case in that not only F_1 in reciprocal crosses is different but also the segregants in F_2 are carried in one direction by the cytoplasm. In our case, this direction was the direction toward the maternal type from which the cytoplasm sprang: light cytoplasm, for example, made all gene combinations lighter. In Sirks' case, however, the minor cytoplasm generally increased the action of certain growth genes but decreased that of others; similarly with color genes. This difference between the two cases cannot, however, be considered as of primary importance. The subspecies of *Lymantria*, which were used, are distinct natural forms, isolated from each other and therefore presumably well balanced in themselves through long selection. The subspecies of the beans, however, are cultural varieties and therefore probably not so distinctively balanced. It must be stated that, unfortunately, in Sirks's cases, the analysis of further extracted generations is missing.

We mentioned previously the fact that all the cases of plasmatic differences thus far known and recognizable by genetic methods were found in crosses involving at least subspecies. This does not mean, however, that all such crosses must give this result. Baur (1932), for example, reports that in his numerous crosses between geographic so-called species of *Antirrhinum*, no reciprocal differences were found. But as this material has not yet been worked up quantitatively, later work might change this statement. There has come to my attention, however, only a single case in which positive results have been found in an ordinary cross with mutations. Kuehn (1927) reported the isolation of a strain of the wasp *Habrobracon* differing in intensity of body pigmentation from the stock. In crossing this form to the type, he reports results that practically repeat our results in *Lymantria* and are represented sufficiently by the diagram given above, with the exception of multiple genes being involved.

We have dwelt thus far mostly upon cases in which the conclusions regarding plasmatic influence upon the gene-controlled phenotype could be tested at least in the F_2 generation. But

there is an additional set of facts derived from species crosses in plants, where no F_2 generation is available. Most of this work has been done in crosses between *Epilobium* species by Renner, Lehmann, Schwemmle, and Michaelis (see Michaelis, 1933-1936). We shall try to isolate the decisive facts from the considerable body of details, facts that, however, are more nearly related to the experiments in merogony than to those discussed thus far and still complicated by the fact that one of the characters that has been studied is pollen sterility. (A more detailed review and discussion are found in East, 1934.) Crosses between different species may be reciprocally different. If they are different, certain quantitative characters are always involved, which appear to be inhibited in one cross. But within one species are also found different biotypes which show this reciprocally different inhibition after crossing. If a hybrid is backcrossed to the paternal species, and this is repeated over and over again in succeeding generations, finally plants are secured that contain practically only paternal chromatin within maternal cytoplasm. All their species characters resemble, in fact, those of the paternal species, but the inhibitory action on quantitative characters, like corolla length and pollen fertility, remains constantly on the maternal side, as in F_1 .

It should be added as a remarkable fact that the cytoplasmic influence is stronger upon the haploid characters. Pollen fertility reacts much more strongly to a foreign cytoplasm than sporophyte characters (see Michaelis and Wertz, 1935). No doubt a plasmatic influence upon gene-controlled characters is visible in this case. Later, we shall mention some additional details.

Let us try now to find out the general features of the facts just reported. The following conclusions seem to be warranted:

1. A considerable number of known cases show that the action of the genes in controlling hereditary traits is different, when the same genes are working within a different cytoplasmic substratum. In some cases, this is known for definite genes; in others, only for the whole genic outfit.

2. The action of the cytoplasm might consist in shifting the genotype toward the type of the parent that has furnished the cytoplasm, *i.e.*, the mother. It might also consist in inhibiting the action of single genes or of all genes, if they are situated within a definite foreign cytoplasm; this inhibition might act

only if the genes or whole chromosomes in question are present in the homozygous condition, but in other cases also in the heterozygous one.

3. Very few, if any, cases are known in which this differential action of the cytoplasm is found in crossing different varieties or mutants of one species. But the cytoplasmic difference appears rather frequently if subspecies and still more distant forms are crossed. As far as evidence goes, it seems that its effect upon the action of the genes increases with taxonomic distance.

4. In one and the same case, not all gene-controlled characters show the cytoplasmic influence. If we leave out of consideration general actions of inhibition and also complete incompatibility, it seems that such characters are most likely to be affected by the cytoplasmic background, which are of a quantitative nature—size of organs or parts, amount of pigment, shapes of parts, and similar characters.

It would be important to know whether or not specific properties of the cytoplasm exist (aside from the serological specificity) that are different in forms with a cytoplasmic action of the type just considered. Dellingshausen (1935) attacked this problem in Michaelis' *Epilobium* material. The protoplasm of *E. luteum* turned out to be more permeable to potassium chloride, glycerin, and succinimide than *hirsutum* plasm. The permeability for urea is decreased by chloral hydrate in a different way in the two species, a fact that is accounted for by a different size of pores and the presence of different lipoids in the two species. These properties remained constant in 12 generations of backcrosses and are therefore actually cytoplasmic. The interesting observation of Michaelis (1935) belongs here, that *E. luteum* is resistant to mildew; *hirsutum*, not; while *luteum* plasma with *hirsutum* genom are almost resistant. This difference might, of course, be of a serological order.

D. THE THEORY OF THE PLASMON

This last point now leads to the question whether or not we can derive any generalization regarding the cytoplasmic action under discussion. Apparently, some botanists are inclined to assume that certain hereditary qualities may be transmitted by the cytoplasm in the same way as other characters are determined by the genes within the chromosomes (Winkler, 1923; Renner,

1929). And the introduction of the term *plasmon* by Wettstein for the entity of cytoplasmic action in heredity may be considered an outward sign of such a tendency. I cannot refrain from expressing my opinion that the facts do not encourage such a view (see also East, 1934). Where it was possible in the just-quoted cases to base the analysis upon individual gene-controlled traits, it was shown that no cytoplasmic heredity comes into play but only a differential action of different plasmata as substratum upon the action of the genes in controlling the differentiation of definite characters. I do not think that a single case is known of a definite hereditary character that is determined as such by the hereditary constitution of the protoplasm, aside, of course, from the special case of plastid characters. In only one way can I conceive of the facts that have been reported: I assume that genes act in controlling the differentiation of hereditary traits through the control of chains of reaction of definite velocity. Whatever these reactions may be in individual cases, one thing may be regarded as certain; *viz.*, their velocities will be dependent among other things upon the substratum in which they take place, *i.e.*, the cytoplasm. The specificity of the cytoplasm in question may be physical, *e.g.*, a matter of viscosity or permeability; or it may be chemical like the pH situation; but in any case there is no reason to assume that it is of a type similar to the difference between two genes. It is then not a plasmon, acting in some way as an independent part of the germ plasm, which is responsible for the phenomena in question, but simply a physical or chemical property of the cytoplasm of the species. Its most probable action is the inhibition or, in other cases, augmentation of velocities of gene-controlled developmental reactions, resulting in visible influences of cytoplasmic constitution upon such characters, which are influenced predominantly in their development by relative speeds of differentiation. In addition, of course, a kind of poisoning effect of wrong cytoplasmic surroundings might be involved in cases of sterility and the like.

E. CYTOPLASMIC INHERITANCE AND DAUERMODIFICATION

Arrived at this point, we have to return to a fact that we have mentioned repeatedly, *viz.*, the incomplete knowledge of the behavior of the cytoplasmic influence in further generations of extracted homozygotes. The importance of this point for a final

solution of the problem will become clear if we turn now to the consideration of a possibility of interpretation that has recently been tried rather successfully.

We have mentioned before the fact that cases are known in which the genes obviously influence the behavior of the cytoplasm of the egg, *e.g.*, the case of the dextral and sinistral snails. We must consider, therefore, at this point the question whether or not after all the differences of cytoplasmic nature under discussion are not themselves the products of genic action. Of course, such a simple relation is out of the question because this would result in a type of inheritance like Toyama's so-called maternal inheritance. But there is also another possibility. Jollos (1921, 1924) has discovered the strange phenomenon of *Dauermodification*, in which the action of external conditions changes certain characters of an organism and the change reappears in the next generation in a lesser degree and may continue thus for a number of generations until it finally disappears. A number of such cases in Protozoa and Metazoa are known (see Haemmerling's review, 1929), and in all of them the obvious explanation is that the change in question is a cytoplasmic one, which only slowly, in the course of a few generations, is overcome by the action of the genes, controlling the normal cytoplasmic constitution. The experiments designed to test this interpretation have given consistent results (Jollos), though it should be added that all decisive tests have not yet been performed. Jollos and Haemmerling have pointed to the near relation of this body of facts to those reported earlier. If an experimentally induced *Dauermodification* may need up to 8 or 10 generations to disappear, one might conclude that in the previously mentioned experiments of Michaelis and Wettstein no proof is contained that the cytoplasmic difference between the two forms, which was originally present, remains in spite of the presence of foreign genes. It might be quite possible that longer continued experiments would show that, just as in *Dauermodification* the effect of the stimulus disappears in the course of some generations, so the primary, natural plasmatic differences will slowly disappear under the influence of the genes of another form. This would mean that the primary plasmatic differences of subspecies and species would also be controlled by the genic constitution but would be of such a nature that one series of ontogenetic processes

under the control of different genes would not suffice to change it. As a matter of fact, experiments are available to test this problem. The method is to backcross a hybrid that shows maternal influence over and over again with the father, so that the genes are finally mostly paternal, but the cytoplasm is still derived from the original mother. Wettstein performed this with the species crosses of mosses for a number of generations without finding a change in the cytoplasmic influence. Michaelis, however, who performed the same experiment in *Epilobium*, found that all the characters that showed the cytoplasmic influence continued to do it after eight generations of paternal backcrossing but with a clearly measurable reversion toward the paternal type. This, of course, favors the views of Jollos, which we just represented.

A similar effect, visible even in F_2 , has been found by Honing (1930) in tobacco crosses, involving hereditary reactions to light. In a more recent paper (Michaelis and Wirtz, 1935), Michaelis minimizes his former results and claims that in spite of a certain reversion the luteum cytoplasm has remained typical after 13 generations with a hirsutum genom. There can be no doubt that the decisive work in this field has still to be done.

F. CYTOPLASM AND SEX

We have mentioned thus far only cases in which ordinary somatic characters were involved. But there are additional facts where the possibility of a cytoplasmic influence in sex determination is under discussion, in both animals and plants. Correns (1928) studied the behavior of gynodioecious plants like *Satureia* and *Cirsium*, in which pure females occur besides hermaphrodites, and females pollinated with the pollen of hermaphrodites produce only females. The same result appears if the experiment is performed with different species of *Cirsium*, one of which is exclusively monoecious; the other, gynodioecious. The result, *viz.*, only female offspring, was not changed if in many succeeding generations the females were backcrossed over again to the hermaphroditic form. From these facts Wettstein derived the interpretation that the female plants contained something in their cytoplasm that inhibits the formation of the male organs. It might be said in favor of such a view that also

in the species crosses of *Epilobium*, pollen fertility is decreased by cytoplasmic influence and, further, that a comparable case of male sterility in flax, studied by Gairdner (1929), and another in *Aquilegia* (Skalinska, 1928), found also its only probable explanation (given by Chittenden and Pellew, 1927) in the assumption of cytoplasmic inhibition of male differentiation.

In animals, also, the same problem reappears, *viz.*, in *Lymantria*, but it is much more complicated. The basic fact is that sex is determined by a quantitative relation between female and male determining factors. The male factors are genes situated within the X-chromosomes. The female factor, *i.e.*, the something that carries sex toward the female side, is inherited purely maternally, as is proved by the immense body of experiments on intersexuality. In ordinary crosses, it could be shown that this maternally inherited female factor is not changed in 10 and more generations, and the same is also true when long lines of complex crosses are made, introducing from the paternal side the chromosomes of many different sex races over many generations but leaving the maternal line untouched. The purely maternal inheritance of the factor controlling femaleness is therefore an experimental fact, which has stood more decisive tests than required. Now, in moths the female is the heterogametic sex, so that maternal inheritance may mean either cytoplasmic inheritance or inheritance in the Y-chromosome. Certain genetic facts seemed actually to favor a location within the Y-chromosome.

Later, however, very elaborate experiments (Goldschmidt, 1934c) proved that actually the property called femaleness is inherited through the cytoplasm. But this property was found to differ in different races in a strictly quantitative way. The differences were called the different types of strength of the female determiners.

The proof that this property is inherited within the cytoplasm forces one either to assume cytoplasmic genes, which is improbable, or to attribute to the specific condition of the cytoplasm a specific influence upon the action of the sex-determining genes. Goldschmidt (1934c), following a similar suggestion by Dobzhansky, assumed that the cytoplasmic property, which shifts the balance toward femaleness, is something that controls the level of the threshold for the action of male determining genes. This

assumption makes it possible to bring this cytoplasmic action upon sex into line with other known cytoplasmic activities.

G. GENES CONTROLLING CYTOPLASMIC PROPERTIES

We have already discussed on different occasions some of the facts that show that actually properties of the cytoplasm of sex cells, especially egg cells, may be controlled by genes. It may be useful to recount them again at the end of this chapter, adding also plasmatic properties of the male gametophyte in plants and chromosomal as well as nuclear behavior, which itself is probably under control of the cytoplasm (see Boveri, diminution in *Ascaris*).

1. The spiral arrangement of spindle fibers in mollusk eggs, controlling the dextral or sinistral coil in development (see page 206).

2. All other cases of so-called maternal heredity: Toyama and Tanaka's work on pigments of the silkworm egg; the work of Goldschmidt and Katsuki on abnormalities in the reduction division and subsequent double fertilization in the same egg; and the others quoted on page 206.

3. Boveri's (1904) work on the control of chromatin diminution in *Ascaris* by the cytoplasm may indicate that some of the genes controlling details of chromosome behavior will actually turn out to be genes controlling cytoplasmic behavior. The following cases illustrate this possibility: Lesley and Frost's (1927) gene for control of chromosome size in *Matthiola*; Emsweller and Jones's (1931) gene for control of interstitial localization of chiasmata in *Allium fistulosum*; Gowen's (1933) gene producing diploid or subdiploid eggs in *Drosophila*; Beadle's (1930) gene for asynapsis, (1931) gene for supernumerary cell divisions after meiosis, (1932) genes for sticky chromosomes and pollen sterility.

4. Many genes for pollen characters have been analyzed, *e.g.*, the aforementioned waxy gene (Brink), genes for pollen-tube behavior (Brieger and Mangelsdorf, 1926), and many others.

4. CONCLUSIONS

Thus we conclude that the cytoplasm is mainly the substratum for genic action, in which all those decisive processes take place which constitute development and which are steered by the genes. The specificity of the cytoplasm is therefore one of the

prerequisites of orderly development, and this is tacitly assumed when the action of the genes is being discussed. The specificity of the cytoplasm probably increases with the systematic distance of the forms, and it may find expression in crossing experiments in a different result of the action of the same genes in different cytoplasm. Thus far, however, no fact is known that would force us to assume that specific hereditary traits exist that are transmitted through the cytoplasm and are individually caused by a genetic property of the cytoplasm. The plastids of plants are probably a third independent constituent of the cell in regard to heredity.



IV. THE NATURE OF THE GENE

The existence of the Wild-type gene, as previously mentioned, is assumed only on the basis of the mutant genes. Whatever conclusions upon the nature of the genes are drawn from experimental facts, in the end they must be derived from views regarding the process of mutation. We do not intend to quote every single utterance regarding the nature of the gene, as almost all geneticists have expressed their views at some time more or less completely. We shall report only such theories as have been derived from a large body of facts and which have been tested more or less thoroughly.

There are a few *a priori* considerations regarding the nature of the gene which have been emphasized in a more or less similar way by a majority of the workers in this field (*e.g.*, see Hagedoorn, 1911; Troland, 1917; Goldschmidt, 1920*b*; Muller, 1922; Plunkett, 1926; Wright, 1925; Koltzoff, 1928; Mittasch, 1935; Schmalfluss *et al.*, 1928*ff.*). A gene is supposed to have the following characteristics:

1. It is a highly active substance, and it is potent in very small quantities.
2. The substance of the gene is doubled before each cell division; it is therefore capable of assimilation and growth.
3. The gene is able to undergo a definite, sudden, and in many cases reversible change, called mutation.
4. The mutated gene is perpetuated in the same way, is as stable as the original gene, up to the moment of another mutation.

The first two points are accounted for best by the assumption that the gene has the chemical properties of a catalyst (including enzymes) and more specifically of an autocatalyst, which reproduces itself as one of the end products of the catalyzed reaction. Hagedoorn (1911) was the first to elaborate this idea, which has since reappeared more or less independently in the writings of the authors quoted above. This interpretation of the gene, which defines only its type of action in terms of chemical kinetics, is independent of all the special ideas that have been elaborated to

account for points 3 and 4 of the foregoing enumeration. At the present stage of our knowledge, we may assume, then, that a gene, whatever it is, behaves in the way of an autocatalyst, catalyzing all those reactions which we have studied in the preceding chapters.

To account for the facts of gene mutation and the details of gene action, special assumptions have to be made, the more important of which will now be analyzed.

1. THE GENE AS AN ACTIVE MOLECULE OR GROUP OF MOLECULES

As the gene behaves as a unit in heredity, a unit located at a definite locus in a chromosome, the simplest and most obvious conception of its nature is the assumption that it is a separate particle of matter, *i.e.*, one or more molecules of a substance. If this is the case, a number of possibilities are given for the explanation of the process of mutation. The most important ones, at the present stage of chemical knowledge, are as follows:

1. A mutation is a change in the quantity of the gene, *i.e.*, from x to y molecules (Goldschmidt).

2. A mutation is a complete change from one molecule into quite another.

3. A mutation is a partial change within the molecule, one residue or side chain being replaced by another one (Guyer, Correns, Demerec).

4. A mutation is a change within the tridimensional arrangement of a molecule, *i.e.*, the formation of a stereoisomere (Karczag).

5. A mutation is a quantitative change, not by simple addition or subtraction of individual molecules but by polymerisation, the formation of chain molecules (Baur, etc.). We shall review these possibilities after adding a few remarks concerning the number of genes.

Authors who assume that the gene is a molecule or a small group of molecules are naturally interested in proving that the size of the gene is of the order of magnitude of protein molecules. Though calculations of this type may not seem so significant now that it is known that chain molecules exist having a magnitude of 800 to 1000A. length and more (see page 293), the facts may be briefly mentioned. Estimates of the number of genes

in a chromosome have been made repeatedly. Morgan and his colleagues did it in a more general way. Muller (1928a) calculated from the frequency of unequal crossing over in the Bar locus. Muller and Prokofieva (1935) made a new calculation; Bridges drew conclusions from the number of bands in the salivary chromosomes (*ca.* 3540); Shapiro and Serebrowskaya (1934) and Berg (1934) measured mutation rate as compared with chromosome length excluding the inert regions. The most elaborate calculations have been made by Gowen (1933), who used data on the frequency of mutation, both visible and lethal, after irradiation with different doses and calculated on the basis of the probability of single hits. Assuming the existence of 175 visible, viable sex-linked genes in *Drosophila* and finding 7.3 times more recessive lethals in the X-ray experiment, he had to assume 1280 loci for these genes. Furthermore, 960 loci must be assumed for dominant lethals on the same basis of estimation. From the effect upon the autosomes, taking into account their relative mass, a similar calculation for the autosomes is made, which leads to large numbers, as Table 21 shows:

TABLE 21
(From Gowen)

Type of loci	Number	Per cent
Sex-linked loci of visible factors.....	175	0.6
recessive lethals.....	1,280	4.7
dominant lethals.....	960	3.5
Autosomal loci of visible recessives.....	1,800	6.6
recessive lethals.....	13,100	48.0
dominant lethals.....	9,800	36.0
All chromosome loci of dominant visibles.....	175	0.6

If it is taken into account that not all these mutants will appear at different loci, the minimum count for genes is 1,280 for the X-chromosome and 13,100 for the autosomes. From these data the size of the gene may be calculated. The upper limit is set at 1×10^{-18} cm.³ from physical considerations. The actual size, as computed from the size of the chromosome, would be 10^{-6} cm.³ This, according to Gowen, would allow for something like 15 protein molecules.

A. MUTATION AS CHANGE IN QUANTITY

This interpretation of gene mutation has been derived by Goldschmidt (since 1916) from the following facts and deliberations:

1. There is a basic difference of action between one and two sex-determining genes, showing that the dosage of the gene is important for its action.

2. Intermediate conditions are found, showing that an orderly series of effects exists between the action of one and two sex genes (intersexuality). In this case, these actions may be described in terms of intermediate quantities (between 1 and 2) of sex genes. This enables one to predict the results of any possible combination or addition of different sex genes, results that were consistently obtained. For this reason, it could be concluded that the different potencies of sex genes, varying between the potencies of one or two actual doses, were dosage differences themselves.

3. It was shown that the different quantitative combinations of sex genes acted by controlling developmental reactions of definite velocity, which were proportional to the assumed relative quantities of the sex genes. The simplest assumption that one can make regarding the action of an active substance, *ceteris paribus*, is that it follows the mass laws in which one variable is the quantity (concentration) of the catalyst. The assumption that this is the meaning of different gene quantities would therefore link the action of the gene to elementary facts of chemical kinetics.

4. It was found that many cases exist in which the effect of actually different gene doses is roughly proportional to the dose.

5. It was found that series of conditions of genes exist, the multiple allelomorphs, in which frequently the effects are proportional to a simple seriation of the genes in question. The differences of these alleles may be called their *potencies*; if compared with the other facts, they may be considered actual dosage differences.

6. It was found that in the cases mentioned under 5, the effect in heterozygotes and compounds frequently appeared to be consistently equal to the added effects of the respective simplex genes.

From such facts, many details of which have been reported above, Goldschmidt concluded that the majority of mutations

of the gene consist in changes in its quantity, say from 5 to 6 or to 10 molecules or from 5 to 4 or to 2, etc., molecules. This, again, presupposes that the quantity of a gene (the number of molecules) is as constant as its quality and that a mutational change in quantity leads to a new equilibrium.

This theory has been criticized with a number of objections, many of which are not relevant because based upon misunderstandings. To mention only one: it has been argued (Muller, 1932*a*; Timofeeff, 1933*a*) that the existence of reverse mutations excludes the quantity idea. It is difficult to imagine what is actually meant by such an argument. If it is possible that the typical quantity of gene molecules is controlled by the underlying chromosome mechanism, and if gene substance is produced as a result of gene action (autocatalysis), an idea without which no theory of the gene can work, the number of these molecules may increase or decrease, whenever the equilibrium is disturbed (this is the meaning of *mutation*).

More serious are the following objections:

1. From the standpoint of chemistry. It was pointed out by Wettstein (1924*a*) that typical changes in the velocities of reactions could be produced, *e.g.*, by a change in pH. Schmalfuss (1928*ff.*) performed many model experiments with melanin formation and showed that models can be made up in which differences in the quality of the chromogen or the oxydase might lead to different quantitative results in regard to melanin formation. The correctness of such statements is obvious and coincides, after all, with everyday experience. If, for example, growth is controlled by a vitamin and by a hormone, their combined effect is quantitative. Multiple factors, which probably are different in quality, also combine to make a quantitatively different action. But such facts have nothing to do with those cases from which the theory has been derived, in which some members of the series are actual quantities, a fact from which an inference is extended to the other members. The only conclusion that may be drawn from criticism of the type here discussed is that many cases are known in which the gene acts proportionally to its actual quantity. Also, there are many other cases in which it is possible to draw an inference from the knowledge of the action of actual gene dosage upon intermediate effects of other gene conditions as due to intermediate quantities

of the gene; but in no other cases can it be proved that mutational changes are of a quantitative nature. This conclusion, of the agnostic type, is unassailable, as agnosticism usually is, but it is not constructive.

2. From an evaluation of the facts concerning pleiotropic action of genes (Dobzhansky, 1930; Muller, 1932; Stern, 1930). These facts were discussed (see page 89), and it was shown that there is no reason to assume that very different developmental processes must be affected in a perfectly parallel plus-minus seriation, as threshold conditions and numerous interactions come into play. A perfectly parallel change in regard to different processes, affected by the same gene and its allelomorphs, is actually expected to be the rarer occurrence. Wright (1916), who found the first case of nonparallelism, realized that the explanation has nothing to do with the gene but with the genetic and other environment in which different developmental reactions take place (see page 88).

3. The most serious general criticism of the theory discussed here is that it is very difficult to imagine a physicochemical mechanism that controls the constancy of the number of gene molecules in the different loci of a chromosome. Goldschmidt (1917a) had pointed to some possibilities, but their realization would require very difficult assumptions indeed. Later, (1932a) Goldschmidt returned to this problem and pointed out that new developments of chemistry could supply a better model. To this point we shall return later (see page 293).

We may draw the following conclusions:

1. Actually genes may act in proportion to their quantity, and this relation is, *ceteris paribus*, of the same type as that found in the kinetics of chemical reactions.

2. In some cases, what has been described as different allelomorphic conditions of genes has turned out to be a series of actual quantities of chromosome material (Bar, deficiencies).

3. In some cases, the facts permit the inference that gene mutations are actually changes in the dosage of the gene.

4. The conclusion that mutations are generally of the type of a quantitative change in gene substance would have to be supplemented by the still missing demonstration of the mechanism to control constant quantities. Modern developments of the gene

concept may, however, lead to a reconsideration of all these points, as will become clear later.

We may point finally to an important point. Since the gene must needs give rise to two daughter genes of the same constitution in cell division, it is generally assumed that the gene divides into two like an organism. In Goldschmidt's theory, this is not the case, but the cell produces as a consequence of the autocatalytic action of the gene more gene molecules, of which an equal number is adsorbed to the daughter chromosome at the time of division of the chromosome. In a recent paper, Haldane (1935), who is opposed to the theory of gene quantities, comes to the conclusion that the gene is something specific which cannot consist of many similar parts because it might be activated by a single light quantum. Therefore, it cannot reproduce by fission. From a biological point of view, one might speak of a parent and two daughter genes. From a chemical point of view, one must think of a model gene and a copy of it produced in the cell. For an explanation, Haldane looks forward to wave mechanics. Similar views have also been expressed by other authors (Koltzoff, 1935, see page 301).

B. MUTATIONS AS CHANGES OF SIDE CHAINS OR RESIDUES

A set of facts that has led to numerous speculations regarding the nature of the gene is found in the occurrence of what are called nowadays unstable genes. The facts were discussed by De Vries (1903). They were later taken up and analyzed by Emerson (1914, 1917, 1922) and Correns (1905, 1919, 1928) and more recently by Anderson and Eyster (1928), Eyster (1924-1929), Demerec, (1928*ff.*), Imai (1925*ff.*), *et al.* Correns (1919) seems to have been the first to draw inferences concerning the nature of the gene. A recent review of the literature on unstable genes has been given by Demerec (1935*b*). The most typical cases are found in plants where a peculiar variegation is caused by unstable genes. Generally speaking, they are produced by a single mutant gene, which must, however, undergo some changes during individual development, which may be described in general terms as somatic mutation. It occurs most frequently as a reversal toward Wild type but also toward intermediate conditions. The details are rather complicated, as the following description of the phenotypes by Eyster (1928) shows:

A continuous series of quantitative variations ranging from apparently deep self colors with only occasional color changes that are apparent through a series of dilute self colors with all gradations of color from deep red to whitish and with increasing numbers of dots, splashes, lines, bands and larger segments of darker and lighter colors; and through a series of variegations varying in pattern from very heavy to extremely light.

It is obvious that a hereditary return to Wild type is effected when an area with the return mutation embraces the germ cells. Only rarely reversible mutations of these unstable genes occur, but changes to different alleles are found. Many factors seem to influence rate and type of somatic mutation in these unstable genes.

Correns (1919) described this instability as a disease of the gene and makes the following assumptions: The gene consists of a large molecule to which the same side chain of atoms (same residue) is attached, say, ten times. This number might undergo changes in the plus or minus direction under unknown conditions, external to the gene. In the case investigated by him, a definite ratio of white and green mosaic spots in the plant would be correlated with the different number of side chains in the molecule. Though Correns did not develop from this a general theory of gene mutation, and though he did not actually consider these unstable genes identical with normally mutating genes (he actually was opposed to this idea; unstable genes were sick genes to him), it is obvious that one might conceive of mutation also as of a quantitative change in the side chains of a gene molecule. (The facts could of course be as well described in terms of instability of the number of whole gene molecules (see Goldschmidt, 1928*b*). From the same body of facts Demerec (1931*b*) derived a related theory of gene mutation, probably also held by many other geneticists who have not enlarged upon it.

Demerec starts from the rate of mutations. This is normally rather low, but all transitions lead from rather stable genes to very unstable ones. In the latter, the rate of change is sufficiently high to be measured, and the effects may be easily observed in regard to time of occurrence (the coarser or finer type of variegation), factors affecting the rate, and the end products. According to Demerec, the end product of the change is always the same, *viz.*, change from mutant into Wild-type

allelomorph. (In ordinary mutation, however, it is the other way round, and reverse mutations occur, spontaneously or induced, less frequently.) The change is further favored by the environment and may occur only in certain tissues, and it is also favored by the presence of definite genes. These facts induce Demerec to assume, as Correns did, that the gene is a single organic molecule, complex, of course, but in general constitution not different from known larger molecules. We have mentioned the case studied by Demerec in *Drosophila virilis*, the unstable gene for Miniature wing, which forms a multiple allelomorphic series, two members of which are unstable. No change from one allele into another occurs; but within an unstable line, changes in the degree of stability are frequent. From this Demerec draws the surprising conclusion that changes from one allele to the other are independent of each other and arise by changes in different groups of a gene. As so many changes of a gene are lethal, and as lethals may reasonably be laid to the actual loss or inactivation of the gene, it might be concluded that only very few changes in the gene molecule can be tolerated. The more or less considerable instability of the gene would then mean the presence of a chemically unstable group. Experiments in treating such unstable genes with X rays or high temperatures had negative results (see, however, Gowen and Gay, 1933), from which it is not concluded that these unstable genes are different from ordinary mutations but that the effect of treatment is too small as compared with the normal rate of change to be detected. The author thinks that the logical conclusion to draw from these facts, as compared with all the other facts, is that unstable genes are a different phenomenon from ordinary mutation, as was held by Correns, who called them *sick genes*. In a general way, one might add that conclusions from the cases here reported upon the normal phenomenon of mutation could be drawn safely only from facts common to both phenomena and not from those in which they differ.

There are a number of facts that show that the problem of unstable genes is far from being solved and that it is quite probable that a phenomenon *sui generis* is involved that might lead to important information regarding the gene and its action. The cases in question would deserve a much more complete analysis, especially with the addition of embryological experimentation.

There is the work of Lilienfeld (1929) on the form of leaves in *Malva parviflora*. A dominant mutation produces an inconstant laciniate type. It is characterized by an inherited tendency to show highly laciniated leaves in young plants which are gradually replaced later by more and more normal and even hypernormal leaves. This, as well as the behavior of heterozygotes, would appear as a simple problem of morphogenesis which could be explained easily by genic action upon the rate of production of something needed for full development of leaves (*cf.* the vestigial case). But the types between laciniate and hypernormal reproduce to a certain extent their kind; the highest grade, hypernormal, may be kept constant, and it mendelizes with Wild type. Thus some condition of the gene must be involved. The details are too different from those in variegation to permit such a simple explanation as somatic mutation to Wild type. Lilienfeld herself accepts Correns' (1919) explanation of the sick gene. Apparently, however, the facts are not sufficiently clear yet, though they suggest the possibility of furnishing important information, if analyzed by new methods. This might also be said of a nearly related case, the "rogues" in peas.

One more case of this type may be mentioned. Anderson-Kottoe (1931) analyzed a very complicated case of variegation in ferns, which looks somewhat as if it involved unstable genes. Visible changes from green to pale tissue occur at the reduction division, in gametophytic and in sporophytic tissue. As the prothallium is a simple and regularly formed structure, the moment of these changes may be exactly determined, and the genetic constitution of a cell may be tested by regenerates from it. The results do not agree with the simple assumption of somatic mutations. It is supposed, moreover, that periodic changes of the gene in question occur, which cannot be of the nature of losses or gains of parts. Anderson-Kottoe formulates a very complicated hypothesis. She assumes that a factor necessary for chlorophyll-formation exists in seven different conditions and that each condition may be stable or unstable. The latter means mutation from one state to another at any point in the life cycle of the plant. Each combination of these states is responsible for a certain phenotype, stable or unstable and different for the phases of the life cycle. From the breeding results, a definite combination for each phenotype is derived, and its mutability as

well as the place of it stated. Thus, a very complicated system is built up, but it would be difficult to state whether or not this is necessary and whether or not one could derive from it conclusions regarding the nature of the gene. A remarkable but not yet completely analyzed fact has been contributed by Kostoff (1935) who finds gene instability in form of variegation after species crosses in *Nicotiana*.

If we think of the discussions at the end of the last chapter (Goldschmidt, Haldane) and the facts presented now, it appears more reasonable to assume that the phenomenon of unstable genes has to do with the method of "copying" the mother gene, which may be visualized in quantitative terms of molecules (Goldschmidt) as well as of side chains (Correns). In this case, either no conclusion upon the nature of gene mutation may be drawn, or only one of a quantitative type.

The first alternative would be realized if Stern's (1935) hypothesis should turn out to be true, *viz.*, that the results ascribed to unstable genes are actually consequences of somatic crossovers after certain chromosome rearrangements, involving also a position effect upon dominance.

C. MUTATIONS AS CHANGES OF A STEREOISOMERIC TYPE

If the gene is a molecule, or a group of identical molecules, a mutation might possibly occur through the formation of stereoisomeres. As a matter of fact, some writers actually speak of mutant genes as stereoisomeres. I do not know, however, of any geneticist who has tried to derive such a hypothesis from special facts, and thus far no facts seem to be known that could be better coordinated by this idea than by any other. A chemical fact might be mentioned, however, in this connection. According to Ruzicka, the stereoisomeres of the male sex hormone have no hormonal effect at all, whereas many of the isomeres of the female hormone act alike. This one example demonstrates that it will be difficult to find rules regarding stereoisomeres which will enable one to describe the genetic facts in simpler terms, *i.e.*, to explain them (see also the theory of Karczag, 1928).

D. MUTATIONS AS POLYMERIZATIONS

The idea that mutations might be polymerizations (or depolymerizations) of large organic molecules has been used by Baur

(1924) to interpret series of multiple allelomorphs. This is, of course, only a modification of the view that the quantity of a gene is changed by mutation, as such a quantitative change might as well be an increase in the number of free molecules as a polymerization. All the arguments applying to one theory therefore apply also to the other. But some of the recent developments in chemistry may lead to a reconsideration of these different types of quantitative views. The work done on chain molecules (Meyer, Mark, Staudinger) and their micellar conglomerations might furnish a new model of the gene, capable of quantitative changes, as Goldschmidt (1932*a*, 1934*c*) and also Koltzoff (1934) pointed out. No elaboration of such an idea is yet available. But the same idea may lead in still another direction, as will be shown below.

2. THE THEORY OF THE GENE AS BASED UPON PHYSICAL CONSIDERATIONS

The work on production of mutations by X rays, inaugurated by Muller, has naturally appealed to the physicist, who was induced to compare the action of X rays in physics with that of the same agent upon the gene in producing a mutation. The most elaborate inquiry from this standpoint has been made in collaboration by the radiologist Zimmer, the theoretical physicist Delbrueck, and the geneticist Timofeeff (Timofeeff, Zimmer, and Delbrueck, 1935). The decisive fact for a physical analysis is the proportionality between X-ray dosis (measured in "*r*-units") and rate of mutability. This proportion is a perfectly linear one, as was proved first by Hanson and Heys (1929). The second important fact is that the same rule applies to radiation of different length (γ rays), demonstrating that the effect is independent of the wave length. From the genetic side, the important points are that mutations are reversible and, further, that different "genes" react differently upon radiation. Zimmer now assumes that the biological effect is produced in any case by hits, whichever of the different theories in this field is used. The facts of proportionality to dosis, just mentioned, may be expressed by the equation $x = a(1 - e^{-kD})$, in which x = number of mutated genes, a = number of irradiated genes, D = dose of radiation, k = a velocity constant, e = base of natural logarithms. This empirical equation is compared with the general

equation covering all cases of effect by a definite dose upon X areas out of n possible areas. He finds that the empirical equation is identical with the general one if the number of hits is one. From this he concludes that one hit suffices to produce a gene mutation (as had also been assumed by others). He proceeds to compare the consequences of the empirical facts with the different theories of biological action of radiation. The fact that the effect is independent of the wave length leads him to the conclusion that the decisive effect is the formation of a pair of ions by the hit, because this formation is independent of wave length by definition (ionization = measure of dosage). One excitation, then, is supposed to be necessary for a gene mutation.

These facts are used by Delbrueck for the construction of a model. It has to be supposed that the gene is a very stable molecule, *i.e.*, a combination of atoms with definite positions and electronic conditions. Such a system might be changed in different ways, the most important of which is the dissipation of energy of excitation of an electron. This leads to an ionization in the neighbourhood, *i.e.*, a rearrangement of the atomic complex by a single elementary process in the sense of the quantum theory. A comparison of the energetic consequences of this view with the facts of mutation furnishes a qualitative agreement of both.

The general conclusion is drawn that mutation consists in a change of equilibrium of the atoms of a molecule, produced by the influx of energy from the outside or the oscillations of temperature energy always present. In detail, this process is assumed to show parallel behavior to photochemic processes. The primary process of absorption of a quantum might lead to very different secondary processes, such as simple steric rearrangements or dissociation of definite bonds setting free a reactive radical. A new residue may be attached from the surroundings, and thus the whole molecule may be changed. From these deliberations it follows that the gene itself must be represented by such an indivisible atomic combination or molecule. The authors make it clear that these conclusions are independent of any assumption as to whether a gene is a unit or a part of a whole. We shall later show that the theory of the gene as a unit is no longer tenable. This will not prevent the application of this theory, especially the part which assumes that one of the secondary consequences of the excitation is an atomic dissociation. This theory is then

a statement in exact physical terms of what was more or less clearly implied in all other theories of the gene.

3. THE GENE AS AN AGGREGATE OF DIFFERENT PARTS

In opposition to the idea that the gene is a single chemically active molecule or a group of such, the view has been expressed that certain groups of facts require for their explanation the assumption that the gene consists of different separable parts, or subgenes.

A. THE GENOMERE HYPOTHESIS OF ANDERSON AND EYSTER

This theory was invented by Eyster and Anderson (1924, 1925, 1928) to account for the facts of variegation produced by what are now called unstable genes. The facts have already been reported and analyzed in connection with Demerec's and Correns' interpretation. Anderson and Eyster assume that those facts can be explained only if a quantitative segregation of parts of the gene takes place during development. The gene, then, is regarded as composed of a constant number of genomeres, or gene elements, which may or may not be chemically identical. The usual genetic difference between pigmented and pigmentless forms is given in the genomeres, all the genomeres *C* having mutated into *c*. If, however, only a certain number of genomeres mutate from *C* to *c*, an unstable gene with two types of genomeres is produced. This gene might be divided into its genomeres in somatic mitoses, producing different combinations of genomeres up to a complete separation of the two types *C* and *c*.

It is obvious that this interpretation is a slightly different way of describing the behavior of the "sick" gene. It agrees with Correns and with Goldschmidt in so far as a quantitative element within the gene is required, which may be conceived as numbers of side chains (Correns), numbers of molecules (Goldschmidt), or numbers of genomeres (Anderson). Any of these or similar conceptions will account for the facts, but also any other explanation of genic changes. It can therefore not be considered that the facts lead necessarily to the genomere theory.

B. THE HYPOTHESIS OF THE SEREBROWSKY SCHOOL

We have reported upon the case of step allelomorphism in the scute series of allelomorphs in *Drosophila*. The facts are

presented on page 236, and their interpretation in terms of development was discussed. The main point was that the different scute allelomorphs could be arranged in a definite series according to the pattern of bristles that each allele removed. Each allele acted independently in the compound in such a way that only those bristles were missing in a compound which both alleles affected in common. Let $ABCD$ be four different bristles, and $abcd$ their suppression; then the allele sc^x may produce the pattern $AbcD$, and the allele sc^y the pattern $abCD$. The compound sc^x/sc^y is phenotypically $AbcD/abCD$ and therefore normal in ACD but with the bristle b missing. If we leave out of this formula the symbols for the unchanged bristles, we have bc/ab ; *i.e.*, the areas affected are steplike, and the parts common to both steps (b) are affected. Serebrowsky, Dubinin, and their collaborators Gerschenson, Agol, and Lewit (1929-1931) conclude that this special behavior can be explained only if the steplike arrangement of the bristle pattern as controlled by the different alleles has its counterpart in a similar arrangement of parts of the gene. A projection of the different patterns in the order derived for each two alleles from the common parts in the stepladder would then represent a picture of the structure of the gene, *i.e.*, a structure of a definite length, made up of a series of smaller elements arranged like steps or as a bundle of sticks the ends of which do not coincide.

We have already discussed some of the aspects of the case and mentioned criticism and counter criticism (page 237). *A priori*, there is no clear reason why a pattern of phenotypic effects ought to be projected as a similar pattern into the gene. Such a projection would help in no way to an understanding, since it is impossible to see how a pattern in a small part of a chromosome could control the formation of a parallel pattern upon the thorax of a fly. If this were imaginable, one ought to expect that, in general, the organism ought to be a replica of its chromosome pattern. The old idea of the manikin in the sperm head would be revived. The idea was therefore rejected by most geneticists, some of whom tried to find an embryological explanation for the facts (Sturtevant and Schultz, 1931; Goldschmidt, 1931*b*), whereas others assumed that the basic description was erroneous (Child, 1936). Though the originators of the theory seem to have deserted it now, it ought to be mentioned

because as keen a thinker as Muller still believes there may be an element of truth in it. The newer discoveries regarding the scute locus, however, shift the discussion to a very different field (see page 306, position effect).

It should be pointed out also that it is always dangerous to draw conclusions from exceptional cases without considering whether the complicated phenotypic behavior is not more likely to be caused by developmental conditions than by an assumed property or structure of a gene. Glass (1933*a*), for example, has described a case that he likens to the scute case and from which he draws definite negative conclusions about the gene. He finds in *Drosophila* a mutant facet notch which is an allele of facet but which produces wing notches, without an eye effect. Facet-facet notch heterozygous is normal, except for 0.26 per cent notched flies, which resembles the behavior of some of the scute compounds. Glass uses these facts to criticize the quantitative nature of multiple alleles. But, looking at the case from the standpoint of development, it is easy to conceive that the heterozygote is actually intermediate when different thresholds for the two processes (eye and wings) are assumed, an interpretation that actually goes back to Wright's earliest work.

C. THE HYPOTHESIS OF THOMPSON

Thompson (1925, 1931) derived a theory of the gene from the experimental studies on the Bar locus in *Drosophila*, especially those of the Zeleny school. The general idea is that the gene consists of a main particle anchored in the chromosome, the protosome, to which a varying number of one or more particles, the episomes, are attached. Mutation is due to the loss of one or more episomes and sometimes also to their addition. Two or more episomes of the same kind are attached to each other and form a side chain, and different episomes are attached separately to the protosome. Varying numbers of the same kind of episomes produce quantitative series of multiple allelomorphs. Qualitative series are based upon numerical variation of more than one kind of episome.

It is obvious that this theory contains the combined elements of most of the other theories mentioned. Quantity of active episomes explains the same facts as quantity of gene molecules, and the calculations that Thompson makes from the Bar data

regarding the number of episomes will therefore lead to results exactly consistent with Goldschmidt's calculations on the basis of quantities. For eventual difficulties, the different episomes are at hand to be called in when a purely quantitative point of view is difficult (Infrabar). This theory, which does not seem to have more heuristic value than the others, has now lost its original foundation since Bar has been proved to be a duplication of a chromosome segment. To retain the terminology, one would have to call the whole of the chromosome the protosome.

4. THE GENE AS LOSS OF CHROMOSOME MATERIAL

Serebrowsky (1929) pointed out that gene mutations may not be changes within a so-called gene but actual losses of chromosome material. He assumed that chromosomes tend to stick together and later to break apart again, whereupon small segments are lost. What appears as gene mutation would actually be a deficiency. In fact, actual deficiencies, lethals, semilethals, and visible mutations look like a series of different grades of the same phenomenon, so that with large visible deficiencies at one end, small deficiencies may be the other end of the series, *i.e.*, recessive mutations. Thus, assumptions regarding attachment and breakage, inversions, translocations, and deficiencies are made different aspects of the same phenomenon, and their phenotypic effects in all cases are reduced to the action of a deficiency. In this group would also be included the so-called *gene mutations*. Serebrowsky does not commit himself as to how such a small deficiency (= recessive mutation) is to be understood in terms of genes. A recent theoretical discussion by Hagedoorn (1934) may also be interpreted as of a similar type. Stadler (1932) elaborated a similar idea. He starts from the difficulties in proving that a mutation is actually a chemical change within a gene. In fact, many perfectly good mutations have later turned out to be actual deficiencies. In experiments with X-ray induced mutations, not only the rate of mutation is proportional to X-ray dosage but also the rate of production of deficiencies. A similar parallel exists between the reducing influence of dormancy of the treated cells upon mutation rate and upon rate of chromosome derangements. A discussion of many facts concerning mutation in plants shows that all the results may be interpreted in terms of deficiencies. The obvious difficulties to such a view derived

from the facts of reverse mutation and multiple allelomorphic series do not appear insurmountable to Stadler. Regarding the gene, he thinks that the association of induced mutation with chromosome breakage does not necessarily exclude the possibility that mutations are intragenic changes, for it is conceivable that some change within the gene may be the cause of the break. But the identification of the induced mutations in general as a class distinct from the chromosomal abnormalities is not possible in the experiments with plants. Stadler, like Serebrowsky, does not draw any conclusions from his interpretation of mutation concerning the nature of the gene. It might be assumed that he took it for granted that small deficiencies may be regarded as the loss of one or a few genes, whatever they are. Serebrowsky, as we have seen, had definite views about the gene (the step structure) which, however, were not derived from the evidence regarding deficiencies.

In a former chapter (see page 176), we discussed Demerec's work with induced small deficiencies in *Drosophila*. Of the large number that he tested, all but one were cell lethal. This excludes all these deficiencies from being of the same type as recessive mutations. The latter, then, must be assumed to be still smaller deficiencies if Stadler's views are correct. We shall return later to this problem, the significance of which lies in a different direction.

5. THE GENE AS PART OF A HIGHER UNIT

The ideas regarding the nature of the gene, as thus far reported, are based upon the assumption that the gene is an independent unit, a molecule or a group of molecules, attached to the chromosome at a definite locus. The chromosome, *i.e.*, its essential part, would have to be visualized as a string of genes, comparable to a string of beads, in which the bead is a unit and the string a different thing. This does not necessarily include the concept that these beads, the genes, are completely independent of each other. Muller (1932) has occasionally spoken of intrachromosomal balance, which would mean a certain relation of interactions of genes within a chromosome as different from those between genes in different chromosomes. Schmalfuss (1929) when discussing chemical models of genes pointed out that the relative position of gene molecules might have an effect

upon their action without any other change. His model is two molecules with side chains of opposite activity, which when very near together might neutralize each other though not if distant. This would be a model for what is called now the position effect, which also indicates that individual genes are not independent from one another. (Details will be discussed later.)

A. THE GENE AS A SIDE CHAIN OF A MOLECULE

Actually, theories of the gene have been conceived that regard the gene only as a part of a whole. Repeatedly geneticists have declared that they consider the chromosome itself as a giant molecule, the side chains of which represent the genes (Castle, 1919; Reimer, 1920). Koltzoff (1928) has elaborated this idea. To him (as to many geneticists) the chromatic part of the chromosome means nothing but a substratum which surrounds the essential part of the chromosome, a chromatic thread representing the gene string of other authors. This is either a very long protein molecule or a bundle of such molecules around which new molecules are assimilated from the surrounding chromatin mixture so that the bundles grow and may divide. In these long molecules, the many different radicals have their definite position, and all chemical changes in these radicals, *e.g.*, removal of one or the other atom or replacement by another residue, will appear as a mutation.

It is obvious that this view does not make it easier to understand genic action. Its importance is that it constitutes a first step toward a definition of the gene as a part and not as an independent unit.

Koltzoff (1934, 1935) has repeatedly returned to his ideas and modernized them. He compares (page 293) the recent developments in chemistry with his views and brings them in line. The chromonema or gene string or genonema is a chain molecule (or micella composed of such molecules) containing protein and other radicals, the genes. From the surrounding solution these radicals attract their like and synthesize them, assimilate them. The surplus of assimilated molecules, *i.e.*, the genes, their parts, or complexes, pass into the cytoplasm, and thus the genes produce their effects. Complicated and necessary substances like sterols and agglutinins are also supposed to be actually present as genes, which assimilate their like. It may be added that more specific

views regarding the genes themselves are not expressed in these papers.

Apparently, Goldschmidt (1930) was the first to point to certain recent developments in chemistry which could lead further, as did also Koltzoff (1934, 1935) as mentioned. Quoting the work on the chemical structure of fibers (Meyer and Mark) which showed that large chain molecules of measurable length combined into a micellar bundle make up these structures, he pointed out that genes may turn out not to be free molecules but molecules combined into a micellar structure. He alluded to the possibility that the "quantity of the gene" might thus turn out to be the number of links in a chain molecule. In another paper (1932*a*), he says: "The latest developments of organic chemistry suggest a different relation which is also of a quantitative type and nevertheless capable of being produced by the addition of a single quantum: changes in the length of members of a chain molecule in both directions. I shall not develop further this idea, to which I think the future belongs."

The same idea has recently been taken up by a chemist Miss Wrinch, who has developed from it a theory of the gene (1934, 1936), going into the chemical details of what, with Goldschmidt, was only a suggestion and with Koltzoff, little more.

The starting point for Miss Wrinch's speculation is identical with the viewpoint of all geneticists who have tried to advance a theory of the gene. She writes (1936):

The regions of the chromosome of cytology associated with certain genes have become ever smaller and smaller, in some cases being no longer than a hundred angstroms. Simultaneously molecules of the chemist have become ever longer and longer, now reaching a length greatly exceeding 100 angstroms. There is no resting place for the theorist concerned with the structure of chromosomes until his postulates are capable of expression in molecule terms. In a dark forest of facts this at least stands out as clear as day—only with the help of molecular physics is it possible to devise a structure for the chromosome.

The chromosome, then, is a molecular aggregate, and the problem is the chemical nature of the constituent molecules and the manner in which they are arrayed. Wrinch starts with the protein molecule and stresses the fact that the basic molecule is built largely of amino-acid residues and that the active proteins have a high content of diamino acids, especially

arginine. As a model, she takes the clupeine. It is said to consist of long chain molecules, in which arginine residues alternate with certain monoaminoacid residues, 4 or 5 of the former to 2 of the latter, altogether 28 residues, with the length of the chain 98A. Such molecules, placed end to end and held together by suitable bonds in a chain, form the protein pattern of the chromosome, and a bundle of these constitutes a chromosome micella. The individual molecules are different polypeptids, and the pattern may therefore be expressed in terms of side chains of the constituent molecule. The bundle, the micella, may have any width without changing this pattern. Any difference in this pattern, be it of one residue (estimated length 3.5A.) or of one molecule (98A.), would constitute a genetical difference. Wrinch points here to the position effect, which would fit into such a picture. A calculation shows that such a pattern of chromosome length may vary to the number of $10^{50,000}$ patterns. Wrinch then proceeds to find the proper place for the nucleic acid, also present in the chromosome. She views the constitution of this molecule as possessing four negatively ionized centers, which are bound to form basic compounds with the positive amino acid residues. If all four centers do this, and if, as assumed above, all the chains within the micella are identical, the nucleic acid ions will completely encircle the micella. This is the reason why the protein molecules aggregate: they are held together by these nucleic acid ions. This relation may also be expressed by comparing the protein pattern to the warp and the nucleic acid to the woof of a fabric. It may be added that if the nucleic acid molecule is highly polymerized, it may hold together, instead of four, a large number of parallel protein molecules.

In harmony with this concept of the chromosome, Wrinch assumes that a gene is a group of molecules between the natural breakage points, *viz.*, the bonds between the individual chains of molecules. We shall return later to this hypothesis which may also be adapted to a very different point of view.

B. FRIESEN'S HYPOTHESIS OF CHAIN MUTATION

In an earlier chapter we mentioned the hypothesis of Dubinin (page 296) that the gene is composed of subgenes, or centers, which mutate independently; the mutated gene is the sum of

the changes of the centers, which are arranged after the model of steps. The facts were given upon which this concept was based, namely, the behavior of the scute alleles. But it is known that other series of multiple alleles do not exhibit comparable phenotypic effects. In the chapter on multiple allelomorphs, we considered those cases in which manifold effects of multiple alleles seemed to behave rather independently of each other. Friesen (1931), who analyzed one such case, thinks that they must be explained (also the scute case) by the assumption that a single gene never mutates but always a more or less long chain of genes. He speaks of chain mutations, which he believes to be the prototype of mutations. This idea, which it would be difficult to prove, is in principle not different from the subgene concept. In both hypotheses, actual or apparent difficulties in explaining phenotypic effects as due to a single gene-controlled process are surmounted by projecting a corresponding multiplicity into the germ plasm. The subgene theory does it by subdividing the gene; the hypergene theory, as we might call it, does the same by assuming a change in a chain of genes. The same criticism (see page 296) applies therefore to both conceptions. The theory has, however, the significance of showing the growing need of considering the gene only as a part and not as a unit. Friesen actually says that the assumption that genes are united into groups means that they are not independent physicochemical structures but that, in spite of a certain independence, they show some structural interrelations. The same statement may also be found in Brink's work (1932). He concludes from the facts relating to translocations in maize that the chromosome consists of groups of physiologically interdependent genes. Therefore, the propinquity of the genes within a group is essential to normal gene action in a general physiological sense.

6. OUTLOOK UPON THE THEORY OF THE GENE OF TOMORROW

We have mentioned a number of facts that point in the direction of a conception of the gene more as a part of a higher unit than as an independent one. The developments in the last years of genetical research have now led to a point where it has become necessary to ask the radical question: Is not the whole conception of the gene as a hereditary unit obsolete? The facts that make

such an inquiry necessary are grouped around a phenomenon that—rather unfortunately—has been called *position effect*.

A. THE POSITION EFFECT

This phenomenon was discovered by Sturtevant (1925). We have reported in different chapters the details of the Bar-eye case in *Drosophila*. Bar is a duplication of a small segment in the X-chromosome. By unequal crossing over, two Bar genes (if we continue using this term for descriptive purposes) may come together in one chromosome; when homozygous, this is called Double-bar or Ultrabar. At the same locus there is a mutation Infrabar, which also may be obtained by unequal crossing over as Double-infrabar and together with Bar as Bar-infrabar. We have analyzed the quantitative effects of all these combinations expressed in facet numbers and found them proportional to the number of genes present. A combination B/B and a combination $BB/$ have both two Bar genes and ought to have the same effect. Sturtevant found it to be different (see Table 22).

TABLE 22
(From Dobzhansky)

Genotype facets		Genotype facets	
$BB/$	45.42 ± 0.24	B/B	68.12 ± 1.09
$B^iB^i/$	200.2 ± 8.6	B^i/B^i	348.4 ± 12.4
$BB^i/$	50.46 ± 0.40	B/B^i	73.53 ± 1.29

This means that two Bar genes in the same chromosome prevent facet formation in a higher degree than do the same genes in different chromosomes. This might also be expressed thus: Two adjacent Bar genes reinforce each other's action, as compared with two opposite Bar genes. The position of the gene has an influence upon its action.

This effect came into the foreground of genetical interest when chromosome breaks, translocations, inversions, and such rearrangements of chromatin material were obtained by X-raying and studied extensively. Other cases of this effect came to light, and the same term was applied to a number of related phenomena. We may arrange the facts in groups which are not very natural and are only provisional, as new facts are frequently being discovered. Very probably the different groups will turn out to

be only variations of the same phenomenon. All the work was done with *Drosophila*.

1. A first type may be described as follows. At the locus of a known mutation, a break in the chromosome is produced, and a translocation between this chromosome and another chromosome occurs. The new chromosome arrangement is accompanied by a phenotypic effect, described in ordinary genetic language as a mutation, which behaves as does an allele to a known mutation at the same locus with the same type of phenotypic effect. Dobzhansky (1932) analyzed such a translocation. The X-chromosome was broken at the Bar locus, and the left end was exchanged for the right end of the second chromosome. The result was an effect of the type of a Bar allele and was called Baroid. In this case, it could be fairly well proved that nothing else had happened and that the Baroid phenotype is a result of a new arrangement at the Bar locus, *i.e.*, a position effect. (Here the term has a different meaning from the one in the original Bar case: there it described the actual facts; here it implies a definite interpretation. But as the term is widely accepted, it may as well serve for descriptive purposes.)

Since Dobzhansky's discovery was made, other such breaks at the Bar locus have been reported with a corresponding effect. In some cases, it is stated that the break is only near the Bar locus (Offermann 1935). We shall return to this point later. Dubinin and Volotov (1935) produced numerous breaks at the Bar locus by X-raying, many of which—but not all—produced the Bar effect; and Dubinin (1936) described another case of Bar mutation similar to Baroid, produced by a translocation between chromosomes I and II with the break at the Bar locus. Altogether they produced 34 mutations of the Bar type of which 10 proved to be breaks at the Bar locus, 1 a deficiency at that locus, and 6 near by. In the case of 7 incomplete reversions thus produced, 5 had a break at some distance from Bar.

2. The second type of position effect is of the same order as the first; *i.e.*, a break at a definite locus occurs, and the phenotypic effect of an allele of this locus is produced. But in this group the rearrangement takes place within the same chromosome, usually as an inversion. It had been known for a long time that some of the alleles of the scute series were accompanied by chromosome breaks, also alleles of yellow and a few others (Serebrowsky and

Dubinin and their collaborators; Muller, Patterson, and Stone; Beadle and Sturtevant et al.). The work of the last-named group of authors showed that breaks at or near the scute locus were involved. The more refined study of such cases by the salivary-gland method revealed that actually very small inversions were present. Muller and Prokofieva (1934, 1935), Muller, Prokofieva, and Raffel (1935) made such an analysis for the left end of the X-chromosome. They showed that different rearrangements involving the scute locus in *Drosophila*, in the great majority of cases, result in phenotypically different "allelomorphs," whereas nearly identical rearrangements (scute 4 and scute 68) have given essentially the same allelomorphs. Of 27 scute and achaete mutations, 18 were proved to be caused by rearrangements after breaks, and the others are suspected of being the same. One case (scute 19) is a deletion of only a single segment (in the salivary chromosome) with insertion in chromosome 2. Other scutes proved to be inversions of small fragments *in situ*. In this and similar cases, two effects had been observed (double mutations) which thus are referred to the two points of breakage of an inversion. From such facts the authors are inclined to assume that possibly all mutations produced by X rays may be such minute rearrangements.

But such effects are not necessarily bound to minute inversions. Grüneberg (1936) reported upon a very long inversion within the X-chromosome which behaved like an allele of roughest and produced a very rough eye surface. He was able later to get a return arrangement to a normal order in the chromosome, and with it the effect disappeared. What seemed to be a mutation, then, was a position affect.

3. A third type of position effect was described by Dubinin and Sidorov (1934, 1935) for translocations between the fourth and other chromosomes. In this case, the effect of the break does not resemble a gene mutation but a change in dominance, which, of course, could also be described as the production of a mutant dominigene. In flies heterozygous both for this translocation and for the fourth-chromosome recessive *cubitus interruptus*, this latter character appeared as semidominant to completely dominant. Sturtevant and Dobzhansky (Dobzhansky, 1936) tested some more such translocations, so that altogether 48 have been tested, of which 22 showed the dominance effect. Dubinin

performed also the necessary tests to exclude other explanations. He found, further, a similar result for the gene hairy in the third chromosome—in fact, both effects simultaneously, when the translocation involved breaks near both the hairy and the cubitus interruptus loci. In a crossover experiment, Dubinin even claims to have introduced the hairy locus itself into the broken partner chromosome with the result that this replaced hairy gene also showed the dominance effect.

Similar results were obtained by Dobzhansky and Dobzhansky (1933) for the gene bobbed and by Dobzhansky and Sturtevant (1932) for the genes yellow, kurz, rudimentary, and forked. But in these cases duplications were involved, *i.e.*, chromosome fragments containing the Wild-type alleles in addition to the two recessive genes in the normal chromosomes (one + being dominant over two recessives). The increased dominance of the recessives in these cases might have different reasons, usually expressed in terms of disturbance of genic balance. But the remarkable fact is that the dominance-shifting effect is produced only when the duplicate fragment is broken off near the locus of the gene showing the dominance effect. This is certainly in favor of the assumption that here, also, the position effect of the cubitus interruptus type is involved.

4. There are cases that belong to more than one of these categories; *i.e.*, allelomorphic mutations are found as a consequence of translocations, inversions, duplications, and deficiencies. But the decisive point is that, again, the effective locus is near or identical with the point of breakage. A complication within this group of cases is that these effects behave frequently like unstable genes and therefore appear as variegation, mottling. All these cases are phenotypically dominant eye colors, studied first in detail by Muller (1930) and later especially by Glass (1933, 1934) and Schultz and Dobzhansky (1934). Without going into the complicated and not yet completely analyzed genetical details (now checked by the salivary-chromosome method), it may be stated that in the best known set of Plum alleles a break has always occurred near the brown locus in the second chromosome to which all these mutations are allelomorphic and another one near the light locus. According to Schultz (1934), in these cases a transfer of chromosome material to the inert region (chromocenter in the salivary chromosomes) is always involved,

and other authors have confirmed this result. In general terms, we are dealing with the same type of position effect at or near a break, but there is the additional fact that the Plum effect appears only when the material from the brown locus comes in touch with the chromocenter.

5. In a further study of the last-mentioned Plum rearrangements, Dubinin (1936) found what he considers to be a new type of position effect. By further breaks in the inverted region of the second chromosome, which is responsible for the Plum effect by bringing a section of inert material in contact with the broken chromosome, he produced chromosomes in which both ends of the inversion are in contact with inert material. He found that considerable regions on both ends of the inversion produce the Plum effect if contiguous with inert material. The position effect is therefore not a point effect in this case but an effect of different regions. This result ought to be considered in connection with the frequently found position effect not at but near the break.

B. INTERPRETATION IN TERMS OF GENES

Different interpretations have been proposed to explain such facts without changing the concept of the gene. We mention only the idea that in all these cases a mutation arises near or at the locus of breakage, which has been disproved in some of the instances reported; or the idea that small deficiencies are caused at the points of breakage, which also does not agree with some of the facts. The position effect as such has therefore to be accepted, and the problem is, to determine what it actually means. Dobzhansky (1936) expresses himself in a more general way:

The activities of a gene lying in an abnormal position in the chromosome are deflected from their normal course by influences emanating from its new environment but no permanent alteration is wrought in the gene itself. . . . Position effects may prove to be essentially developmental phenomena, but phenomena of intracellular physiology, affecting the coordinates on which the reactions between the primary gene products take place. . . . The hereditary material is discontinuous, for it is segregated into independent units, genes. And yet, it is a continuum of a higher order; since the independence of the units is incomplete, they are changed if their position in the system is altered.

More specific are Muller and Prokofieva (1935) when they assume that position effects are due to a higher degree of interaction between locally more concentrated products of gene activity as compared with the interacting of products from widely separated points, which are either more diluted or changed (see Schmalfuss, page 299). The same idea is also offered by Offermann (1935) and is found in Sturtevant's first discussion (1925). Muller (1935) will not exclude absolutely the possibility of interaction between the genes but thinks that it is more probable that only the products of the genes are involved. In a lecture before the Physiological Congress of 1935, he elaborated this idea as follows. In the production of phenotypic effects, the gene begins by interacting with cellular substances to produce specific products which diffuse from the locus of origin and cause or affect further physicochemical changes. Then follow the chains of reactions and interactions, conceived in the same way as we discussed them above. When such interactions involve the immediate products of neighboring genes there, distance may count. It is to be assumed that the highest concentration of the gradient of gene-controlled primary products will be near the gene, whereas with increasing distance these substances will be altered by undergoing new reactions. This idea has been further elaborated by Offermann (1935).

The important point for the discussions of this chapter is that it is generally assumed that the position effect has to be explained within the present gene theory, which remains unaffected as such.

Muller and collaborators (1935) once were tempted to go one step further, when they argued: "As our studies of mutations in the X and other chromosomes have shown that apparent replicas of practically all known natural mutations in *Drosophila* may also be obtained by X-rays, the further question is raised as to what proportion of natural mutations in *Drosophila* may really be minute rearrangements." The importance of trying to distinguish intragenic from intergenic changes is therefore urged.

C. IS THE THEORY OF THE GENE STILL VALID?

The preceding sentences bring us now to the point where we have to ask ourselves whether or not the theory of the gene as the hereditary unit of actual separate existence is still tenable. The facts regarding position effects, which we mentioned, have led to

a situation where genelike effects are attributed to contiguity between different points in a region of the chromosome, assumed to represent different genes, and the so-called inert material (see the Plum case, above). The theory of the gene has certainly to be stretched considerably to allow a description of such facts in terms of genes. Is there no alternative? It seems that these facts and a number of others, to be mentioned, point to a theory of the germ plasm in which the individual genes as separate units will no longer exist. The gene as a unit is, of course, a concept derived from the existence of a thing called the mutant gene. The normal condition allelomorphic to the mutant condition is assumed to be controlled by the plus gene, when it can be proved that the mutant effect is localized at a certain point in the chromosome, called the mutant gene. But this inference is not necessarily valid. There is a possibility that a condition exists at a definite locus of a chromosome that we call a mutant gene but that no corresponding plus condition exists as a separate unit. Let us assume, with some geneticists (to whom the material was not yet available for a serious discussion of the point), that the whole chromosome is a large chain molecule of complex arrangement. Each point in the chain, *i.e.*, the residue attached at each point, has a definite meaning in the chemical properties and the reactivity of the whole, as is the case with all molecules. (For a detailed model, see Wrinch, page 302 and later discussions of the work of Bergmann.) The Wild type, then, might be controlled by the whole chain as a unit. If the chain is intact, and each residue in its proper steric position, the catalytic processes dependent upon this chain molecule occur in a way that leads to what is called a *Wild type*. Any change in the chain, however, of whatever type, may disturb the normal interplay of the catalyzed reactions, and a deviation occurs which is called a mutation. These changes described in terms of chemical models may be of several types, such as the following: (1) the differences of stereoisomeres, which means that each inversion or other rearrangement within a chromosome would be equivalent to the production of a stereoisomere; (2) the differences in the length of chains as they characterize for example, the different carbohydrates. Each breakage of a chromosome would therefore result in a change of the chemical properties of the molecule; (3) the possibilities of chain molecules composed of

unequal links, the manifold combinations of which form related but different compounds. Translocation would lead to such differences. In general, if the chain molecule (= chromosome as a unit) is needed to produce the reactions controlling the Wild type, any deviation from the typical steric arrangement would change the chemical properties and produce a different type, the mutant, without any change of residues or atoms. As this steric change happens somewhere in the chain, the mutant type is, of course, related to a condition at a definite point or more than one point. Such a point we call the mutant gene. Let us assume that the order in the chain has been changed by an inversion: the new effect appears to be localized at one or both points of breakage, and we might use the word mutant gene for these points, though there is nothing special situated at this point that we could describe in terms of matter, the point being actually a point of reversed order of the old constituents. If, however, no change in the order occurred, we have no possibility of describing this point as a unit of action and therefore cannot call it the Wild-type gene. In other words, there is such a thing as a mutant gene, if we choose this expression for a stoichiometric change at a definite point in a chain molecule, which has the effect of a change in chemical properties, whatever the change may be. But there is no Wild-type allelomorph, only one single normal arrangement of the chain molecule as opposed to all other possible arrangements. The facts of genetics may, of course, be described in terms of genes, but a theory of the germ plasm would have to do away completely with the concept of genes as units. We have intentionally not mentioned the possibility of chemical changes in the individual residues, because the facts, which force us to revise the conception of the gene, are concerned only with steric and stoichiometric changes. Whether or not chemical changes in the residues occur or what may be their role (probably in phylogeny) cannot be derived from the genetic facts thus far known.

The following facts seem to point in the direction of a view regarding the nature of the germ plasm and of mutations of the type as just described:

1. The action of X rays upon chromosomes produces predominantly breaks and the different known rearrangements; the same treatment produces the so-called *gene mutations*.

2. The proportional relation between the quantitative effect of X rays and the amount of ionization is parallel for mutations and rearrangements.

3. Temperature shocks that increase the rate of mutations also produce chromatin rearrangements, in both animals and plants.

4. Mutations induced by X rays and spontaneous mutations are identical.

5. The phenotypic effect of rearrangements, *i.e.*, the so-called position effect, under which must be included all the effects that have been described as mutations occurring simultaneously with rearrangements, is of the same type as the effect of so-called gene mutations. We find all the known types of genic effect. In fact, many effects that originally were regarded as due to gene mutation have turned out to be position effects of rearrangements. Specifically, the following types may be mentioned, using the term position effect now for all phenotypic consequences of whatever rearrangements.

a. Dominant and recessive effects.

b. Effects of the type of a dominigene effect (*cubitus interruptus*).

c. Different position effects produced by different rearrangements involving the same locus behave like a series of multiple alleles (scute, notch, Bar).

d. "Invisibles"—mutations or rearrangements without visible effect.

e. Effects of the modifier type; *e.g.*, the so-called mutant *Beaded* produces alone only a nick in the wing of a percentage of individuals. If combined with an inversion, this effect is modified into the real beaded type. The inversion may be replaced by others in the same region with the same effect, and the removal of the inversion also removes the modifying effect (Goldschmidt, unpublished).

f. Cases in which the effect of the mutant gene is proportional to its dosage. There are chromosome rearrangements exhibiting the same phenomenon, *e.g.*, the Bar case.

g. There is a most remarkable parallel between the spontaneous appearance of so-called gene mutations and effects of rearrangements. Goldschmidt (in press) analyzed a series of cases of complicated rearrangements occurring spontaneously within different lines of *Drosophila*, which led to the appearance of a

number of phenotypes. Some of these behave genetically like ordinary new mutants, a considerable number of others being identical with known standard mutants. If this had not occurred in pedigreed and controlled lines but in an ordinary stock, the impression of a series of simple gene mutations would have been created. Actually a similar case found by Plough and Holthausen (1937) has been interpreted as mass mutation of genes. There are cases in which a number of well-known mutants occurred in a way that is rather suggestive of a similar origin. For example, in *Drosophila*, truncate originated in a Beaded stock; vestigial and balloon, from truncate; spread, from Beaded and vestigial; purple, from vestigial; kidney, from vestigial \times purple; ebony, from balloon. Blistered, jaunty, and curved came from rudimentary (two of which we found to be produced by a rearrangement). Many new mutants appeared among the progeny of crosses between other mutants.

h. It is most remarkable that rearrangements within certain areas have a similar phenotypic effect and might therefore be described as different multiple allelomorphs, *e.g.*, a number of deficiencies near the locus plexus produce so-called *plexates*. Probably some translocations in this region have a similar effect. Duplications and translocations in the Bar region produce the Bar effect; different deficiencies in the fused region, notch effects; point mutations and translocations in the yellow region, yellow color. The similar phenotypic effect of different happenings at one point or in a more or less long chromosome section near this point may in these cases be due to a so-called mutation, a deficiency, a translocation, a duplication.

i. There are cases in which the end members of a series of multiple allelomorphs are suspected or known to be deficiencies (vestigial, eyeless). There are other series of multiple allélomorphs with an additional deficiency appearing as a member of the series, *e.g.*, bobbed.

j. There are certain changes that occur at many different points of different chromosomes, producing a similar phenotypic effect. The minutes in *Drosophila* are such changes, which in part are certainly deficiencies and in part not visibly different from gene mutations.

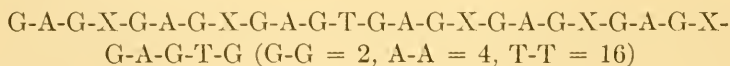
k. There are a few extremely typical "mutants" that we have discussed in connection with the cases of homoeosis. They are

all located in the same section of chromosome III: bithorax, 58.7; bithoraxoid, 59.5; aristapedia, 58.5; proboscipedia, 45.7; tetraptera, 51.34(?).

Though not complete, this list of facts seems to be a formidable one. All points taken together suggest strongly that the chromosome is the actual hereditary unit controlling the development of the Wild type, that purely steric changes at the individual points of its length produce deviations from Wild type which may be described as mutations, even as point mutations, though no actual Wild-type allelomorph and therefore no gene exists.

If such a view, which we consider to be tomorrow's theory of the germ plasm, should turn out to be unavoidable, a number of problems will have to be solved. The first one is whether or not a model of such a chain molecule is available and whether or not it is possible that the different points in its length exercise a different specific, and independent catalytic action. It seems that the most recent work of Bergmann and coll. (1937) on the structure of the protein molecule has furnished such a model (Goldschmidt, in press). It will be found to be nearly related to the other models, especially that of Wrinch, with the advantage of not using the conception of the gene any more.

Bergmann starts from certain facts upon which he builds a chemical hypothesis, and both facts as well as hypothesis appear very helpful for our present purposes. The protein molecule is known to consist of a chain of amino acid residues linked by peptide bonds. According to Bergmann these residues are arranged in a simple order. Each amino acid has its own rhythm different from that of the others, and the superposition of all these rhythms produces the pattern of the molecule. The rhythm itself, meaning that one type of residue appears always separated by a definite number of others in the chain, follows a simple arithmetical rule. Thus silk fibroin which contains glycine, alanine and tyrosine residues shows an arrangement of these in the rhythm:



The total number of members of a chain is 288 or a multiple thereof. To organize such a molecule, a chemical organizer is needed of immense specificity. According to Bergmann the

only known substances with the necessary properties are the intracellular proteinases, which both hydrolyze and synthesize the protein molecule. At this point Bergmann pronounces the hypothesis that the proteinases are themselves proteins. "If the proteinases themselves are proteins and at the same time have the ability to synthesize other individual proteins then there must exist proteinases which have the ability to synthesize replicas of their own structural pattern and therefore are able to multiply in suitable surroundings."

It is astounding to see how these chemical facts and hypotheses fit the requirements for a chemical theory of heredity, as postulated in our previous discussion. Let us assume that the individual chromosome actually is a single immense chain molecule and a proteinase. (This means the essential part of the chromosome—the so-called gene string—to which is added nucleic acid, which makes in some way the stability of the long chain possible. All modern hypotheses regarding chromosome structure have reckoned with these two constituents.

This proteinase then has different effects according to its special surroundings. Either it may produce its own replica, which amounts to a division of the chromosome, or it may synthesize other proteins from the parts present, or it may hydrolyze proteins. The latter two activities would constitute what is usually conceived as being the function of the gene. The immense specificity of this proteinase is based upon its typical structure. This, however, represents a most complicated though regular pattern, composed of the superimposed rhythms of the different amino acid residues. This again means that any breakage or rearrangement in the chain leads to a destruction or impairing of the specificity and therefore to other reaction products, which have to be assumed to control the phenotypic changes. Thus it seems that the latest developments of genetics and of protein chemistry permit the statement of a reasonable hypothesis regarding the chromosome, which could easily be elaborated much further.

Among the facts which will have to be explained on the basis of this new model there is the question how the relations between quantities of what is called a gene and a proportional effect can be explained in terms of steric changes. There is no difficulty in the cases where duplications or deficiencies are involved, as

models are available for a proportional chemical action with different degrees of methylation, etc. As a matter of fact, the concept of the gene, which considers its primary property to be its quantity, will be most easily incorporated into the new hypothesis and will turn out to have been a better guess than most of the other concepts (see page 293). This does not mean, however, that such physical considerations as those discussed above (Timofeeff, Zimmer, and Delbrueck) are not valid. They actually lead only to the conclusion that the elementary quantum process produces secondary changes of atomic equilibrium. One of these is also a dissociation of bonds, which, after all, would also be needed for the breakage of a chain molecule. There is, then, no obstacle from the side of physics to changing the concept of the gene in the direction here espoused. As a matter of fact, I had reached this conclusion years before the physical analysis of the three authors was published (see quotation, page 301).

A second point concerns the problems of how evolutionary changes occur and whether or not chemical changes in the residues as opposed to steric changes in the chain molecule are of primary importance. No facts based on experimentation are yet known that permit conclusions on this point. But it would be a mistake to reject necessary conclusions concerning the gene concept, because they will not lead to an explanation of everything.

Views regarding the gene as developed in this chapter have been "in the air" for some time. Goldschmidt's remarks (1930a) have been quoted, and it may be added that he has discussed the contents of this chapter repeatedly in public during the past years. The *Drosophila* workers, while discussing the position effect, touched upon it; and Muller (1935) almost drew such conclusions though shrinking, as it seems, from the last step, namely the abolition of the gene concept. The chemical models used by Koltzoff and the more modern one by Wrinch are also steps toward the views developed here. It remains for the physico-chemist to decide whether or not the new model could also take care of the independent catalytic actions of what was considered to be a gene.

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